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JOHN SCOTT WILSON

Date of Birth — Date de naissance 13/03/53	Country of Birth — Lieu de naissance CANADA

Permanent Address — Résidence fixe
1224-6th Ave. 'A' So. LETHBRIDGE, ALBERTA

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A. A GENERAL PROCEDURE FOR THE CONVERSION OF RIBONUCLEOSIDES TO 2'-DEOXYNUCLEOSIDES

B. A FACILE METHOD FOR DETERMINATION OF ANOMERIC CONFIGURATION

by

Ⓒ JOHN SCOTT WILSON

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
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A. A GENERAL PROCEDURE
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B. A FACILE METHOD FOR
DETERMINATION OF ANOMERIC CONFIGURATION

submitted by JOHN SCOTT WILSON in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

Morris J. Robins
Supervisor

Byron Kratochvil

D. L. J. Clive

External Examiner

Date October 13, 1981

ABSTRACT

A general and efficient procedure for the preparation of 2'-deoxynucleosides has been developed. Selective protection of the 3'- and 5'- hydroxyl functions of the ribonucleosides was achieved through preparation of 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-nucleoside derivatives. The 2'-hydroxyl group of the blocked nucleoside was functionalized under mildly basic conditions using phenyl chlorothionocarbonate and 4-N,N-dimethylaminopyridine in acetonitrile. Treatment of the 2'-phenylthionocarbonate derivative obtained with tri-n-butylstannane in the presence of a free radical initiator at 80°C gave the 2'-deoxynucleoside derivative in excellent yield. Deprotection was effected under neutral conditions using tetra-n-butylammonium fluoride to give the 2'-deoxynucleoside. High yields of 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxyuridine, 2'-deoxytubercidin and 2'-deoxytoyocamycin were realized using this reaction sequence. Application of the procedure to other secondary hydroxyl groups was equally successful as steroid and carbohydrate examples were also deoxygenated in high yield. Acid sensitive substrates were amenable to this method of deoxygenation as demonstrated by the synthesis of methyl 2-deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranoside from methyl β-D-ribofuranoside.

The similarity and consistency of the ^{1}H NMR spectra of the 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-nucleosides indicated that a relatively fixed sugar conformation existed in these compounds. A representative number of these 3',5' blocked derivatives were prepared from β-ribo, α-ribo, β-arabino and α-arabinonucleoside substrates. It was found that for β-ribonucleoside derivatives, the spin-spin coupling values for H-1' to H-2' were generally less than 1.5 Hz. For α-ribo and β-arabinonucleoside derivatives, spin-spin coupling values for H-1' to H-2' were generally greater than 3.5 Hz. The ^{1}H NMR spectra of the α-arabinonucleoside derivatives unexpectedly revealed a large H-1' to H-2' coupling value. This was thought to arise from a change in the sugar conformation of these derivatives relative to the other examples of the 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)nucleosides studied. A single crystal X-ray analysis of 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine was determined to verify assumptions made from NMR spectra on the sugar conformation of these derivatives.

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TABLE OF CONTENTS

Page

ABSTRACT iv

ACKNOWLEDGEMENTS vi

LIST OF SCHEMES viii

LIST OF TABLES x

INTRODUCTION

A. General Introduction and Survey of 2'-Deoxynucleoside Synthesis 1

B. Recent Developments Pertinent to 2'-Deoxynucleoside Synthesis 22

RESULTS AND DISCUSSION

A. A General Procedure for the Conversion of Ribonucleosides to 2'-Deoxynucleosides .. 39

B. A Facile Method for Determination of Anomeric Configuration 73

EXPERIMENTAL

A. General Procedures 95

B. Syntheses 98

REFERENCES 133

LIST OF SCHEMES

		Page
I	Synthesis of Purine Nucleosides by the Fischer-Helferich Procedure.	4
II	Proof of the Configuration of Adenosine (6).	6
III	Synthesis of Pyrimidine Nucleosides by the Hilbert-Johnson Procedure.	7
IV	Baker's Classic Synthesis of 2'-Deoxyadenosine (10).	10
V	Nucleoside Synthesis Involving a C-2' Participating Group.	12
VI	Synthesis of 2'-Deoxyuridine (38) Involving an O-2→2'-Cyclonucleoside Intermediate.	15
VII	Synthesis of Thymidine (13).	16
VIII	Synthesis of 2-Deoxyadenosine (10) Involving an S-8→2'-Cyclonucleoside Intermediate.	18
IX	Reaction of Adenosine (6) with α-Acetoxyisobutyryl Halides.	19
X	Synthesis of 2-Deoxyadenosine (6) Through S_N2 Displacement at C-2'.	20
XI	Possible Mechanism of Glycosidic Cleavage in the Reduction of a cis-Halo Acetate of Uridine (56).	23
XII	Possible Reaction Pathways of an Alkylcarbonyloxy Radical.	25
XIII	Possible Mechanism of Reaction Between an Alkyl Thionobenzoate and Tri-n-butylstannane.	27
XIV	Synthesis of a 4-Deoxypyranoside Through Reduction of a Thioimidazolide Intermediate.	29
XV	Application of Barton's Deoxygenation Method to Prepare a Branched Chain 2-Deoxyfuranoside.	30
XVI	Homolytic Ring Opening of a Cyclic 2',3'-O-Thionocarbonate Derivative of Adenosine.	32

LIST OF SCHEMES (continued)

Page

XVII Opening of 5'-*O*-Acetyl-2',3'-*O*-methoxyethylideneadenosine (86) and Equilibration of Monoester Derivatives of the cis-Glycol System. 34

XVIII Synthesis of 3',5'-Di-*O*-tetrahydropyranyladenosine (51). 35

XIX Synthesis of 3',5'-*O*-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl) Nucleosides. 37

XX Reaction of 5'-*O*-(*tert*-Butyldiphenylsilyl)-3'-*O*-methyladenosine (99) with Thiobenzoyl imidazolide. 40

XXI Synthesis of 2'-Deoxy-3'-*O*-methyladenosine (106) from a 2'-Thionobenzoate Precursor. 41

XXII Synthesis of 5α,6α-Epoxycholestane (122). 53

XXIII Synthesis of 5'-*O*-(*tert*-Butyldiphenylsilyl)-2'-deoxy-3'-*O*-methyladenosine (124) from 5'-*O*-(*tert*-Butyldiphenylsilyl)-3'-*O*-methyl-2'-*O*-phenoxythiocarbonyladenosine (123). 54

XXIV Synthesis of 2'-Deoxyadenosine (10). 55

XXV Synthesis of 2'-Deoxyuridine (38). 58

XXVI Syntheses of 2'-Deoxyguanosine (11), 2'-Deoxytubercidin (55), 2'-Deoxytoyocamycin (139) and 2'-Deoxysangivamycin (141). 60

XXVII Synthesis of 2'-Deoxycytidine (12). 63

XXVIII Synthesis of Methyl 3,5-Di-*O*-*p*-toluyl-β-D-*erythro*-pentofuranoside (152). 66

XXIX Synthesis of 3-Deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (155). 67

XXX Synthesis of 2'-Deoxy-2'-Deutero-*ribo* and *arabino* Adenosine Epimers from Free Radical Mediated Dehalogenation at C-2'. 68

XXXI Biomimetic Deuteration at C-2' of 3',5'-*O*-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl) Adenosine Derivatives. 70

LIST OF TABLES

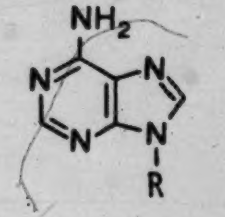
		Page
1	NMR Chemical Shift Data for 3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-β-D-ribonucleosides.	86
2	NMR Chemical Shift Data for α-D-ribo, β-D-arabino, and α-D-arabino 3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl) Nucleosides.	89
3	NMR Spin-Spin Coupling Values for 3'5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-β-D-ribonucleosides.	90
4	NMR Spin-Spin Coupling Values for α-D-ribo, β-D-arabino, and α-D-arabino 3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl) Nucleosides.	92
5	Solvent Dependency of H-1'-H-2' Spin-Spin Coupling Values for Selected 3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl) Nucleosides.	93
6	Calculated and Observed Spin-Spin Coupling Values of 3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)cytidine.	94

I. INTRODUCTION

A. General Introduction and Survey of 2'-Deoxynucleoside Synthesis.

The fundamental unit of higher organisms, the cell, is a complex structure of interconnected elements, each having specific functions. The nucleus is the control center within the cell and contains all genetic information essential for the integrated operation of cellular components. In 1871, Fredrich Miescher[1] isolated a material from the nuclei of pus cells which he called "nuclein". This material was subsequently referred to as "nucleic acid" by Altmann[2] and was found to be common to cells from a number of sources.

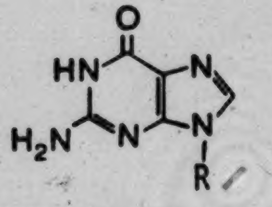
The nucleic acids provide the means for the storage and transmission of genetic information utilized in the synthesis of all cellular constituents. These macromolecules are comprised of polymeric chains of nucleotides linked by phosphodiester bonds. The nucleotide unit is composed of a purine or pyrimidine base, a furanose sugar moiety and a phosphoric acid residue. Levene and Jacobs[3] introduced the term nucleoside to describe the carbohydrate derivatives of purines and pyrimidines isolated from the alkaline hydrolysis of yeast ribonucleic acids. This term has been expanded to include all of the compounds of synthetic or natural



1 R = H

6 R = R′

10 R = R″



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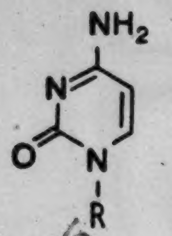

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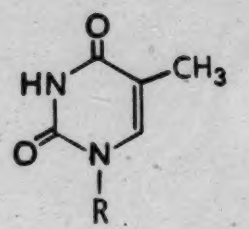

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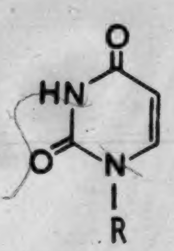

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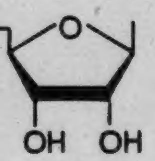
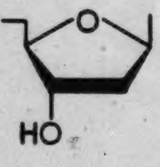


β-D-RIBOFURANOSYL

R″ =



2′-DEOXY-β-D-RIBOFURANOSYL

(2′-DEOXY-β-D-ERYTHRO-PENTOFURANOSYL)

origin which contain a heterocyclic base attached to the C-1 position of a sugar.

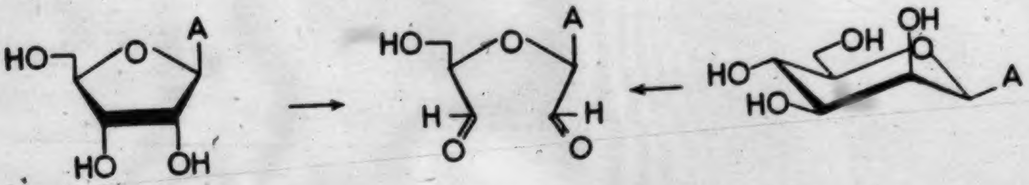
There are two types of nucleic acids, the constituents of which differ primarily in the carbohydrate residue. In ribonucleic acid (RNA) the sugar moiety is D-ribose and in deoxyribonucleic acids (DNA) the sugar is 2-deoxy-D-ribose (2-deoxy-D-*erythro*-pentose). Levene and co-workers[4,5,6] were responsible for the characterization of the sugar residues of RNA and DNA through their exhaustive studies from 1909 to 1933.

Five heterocyclic bases are ubiquitous to the nucleic acids and were first identified by Kossël and co-workers[7] through acid hydrolysis of nucleic acids. The purines adenine (1) and guanine (2) and the pyrimidine cytosine (3) are common to both DNA and RNA. Uracil (5) is found only in RNA, while its 5-methyl derivative thymine (4) is the complementary pyrimidine contained in DNA. The corresponding nucleosides in RNA are adenosine (6), guanosine (7), cytidine (8) and uridine (9) and in DNA are 2'-deoxyadenosine (10), 2'-deoxyguanosine (11), 2'-deoxycytidine (12) and thymidine (13).

The DNA present in the nucleus of all eukaryotic cells contains the information necessary for the biosynthesis and metabolism of the cell. Through the specific ordering of the nucleic acid units in these macromolecules a unique code is established. This code is transcribed to smaller mRNA molecules which act as templates in code translation for subsequent protein (enzyme) synthesis. Chemical inhibition of the biosynthesis of nucleic acids is one major basis of chemotherapy. Bacterial cells and tumor cells divide much more frequently than the cells of the host organism and thus are expected to be affected more severely by an antimetabolite. Routes which are both general and efficient for the synthesis of ribonucleoside and 2'-deoxynucleoside antimetabolites are of considerable importance in this area.

The position of the sugar-base attachment in nucleosides obtained from nucleic acids was first established by ultraviolet spectral comparisons.[8,9,10] Unequivocal conformation of the location of the sugar residue was presented by Todd and co-workers[11] through the synthesis of 9-D-mannopyranosyl adenine (15). Oxidation of this compound with periodate gave a dialdehyde (14) identical to that obtained from adenosine (6).

SCHEME I



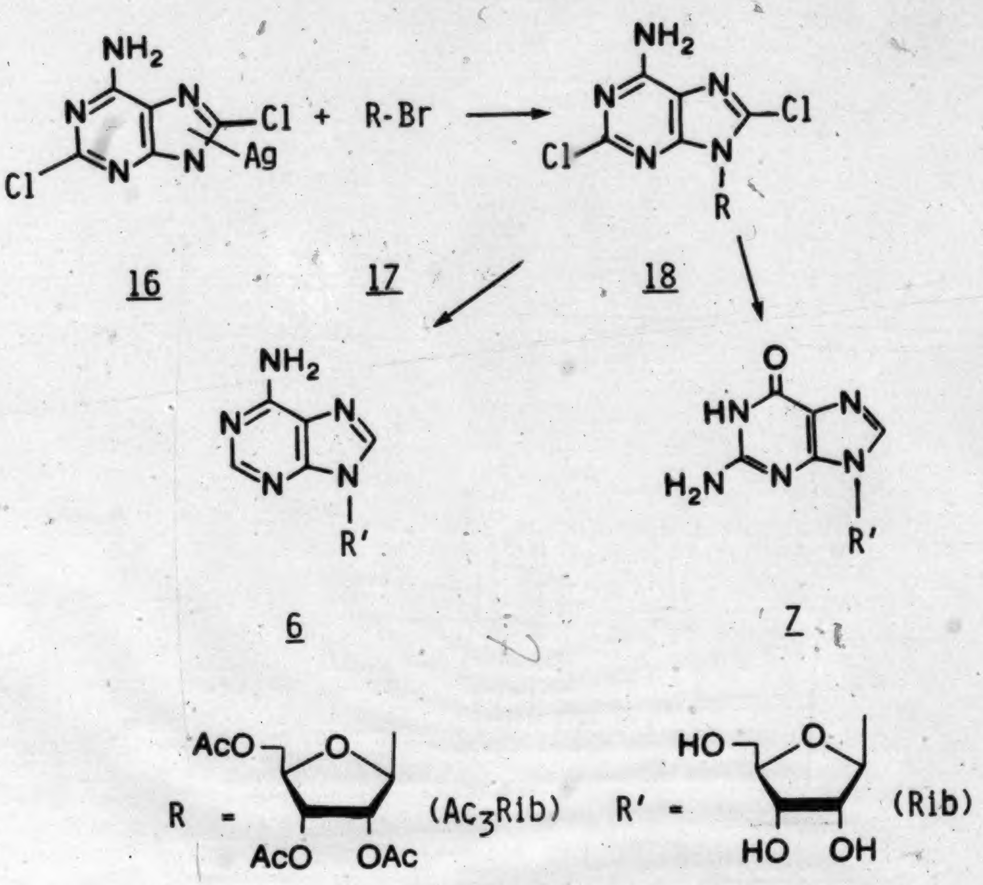
6 14 15

Todd and co-workers[12] also confirmed the assignment of the β configuration of nucleosides by demonstration of the formation of cis-intramolecularly linked 5'-cyclonucleosides derived from cytidine (8) and adenosine (6). Total synthesis of the two major purine ribonucleosides was achieved by Todd's group as the final structure proof.[13] The historical development of the identification and characterization of the nucleosides has been reviewed extensively.[14-19]

The first synthesis of a nucleoside was reported by Fischer and Helferich[20] in 1914 through the coupling of the silver salt of theophylline with tetra-O-acetyl-α-D-glucopyranosyl bromide. The glycosylpurine derivative obtained was later shown to be 7-substituted. This general coupling procedure was utilized by Todd and co-workers[13] in 1948 to synthesize adenosine (6) and guanosine (7), using 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide (17) as the sugar element. The silver salt of 2,8-dichloroadenine (16) was used as the purine component since both the natural purine nucleosides could be made from the 2,8-dichloroadenosine derivative (18) obtained.

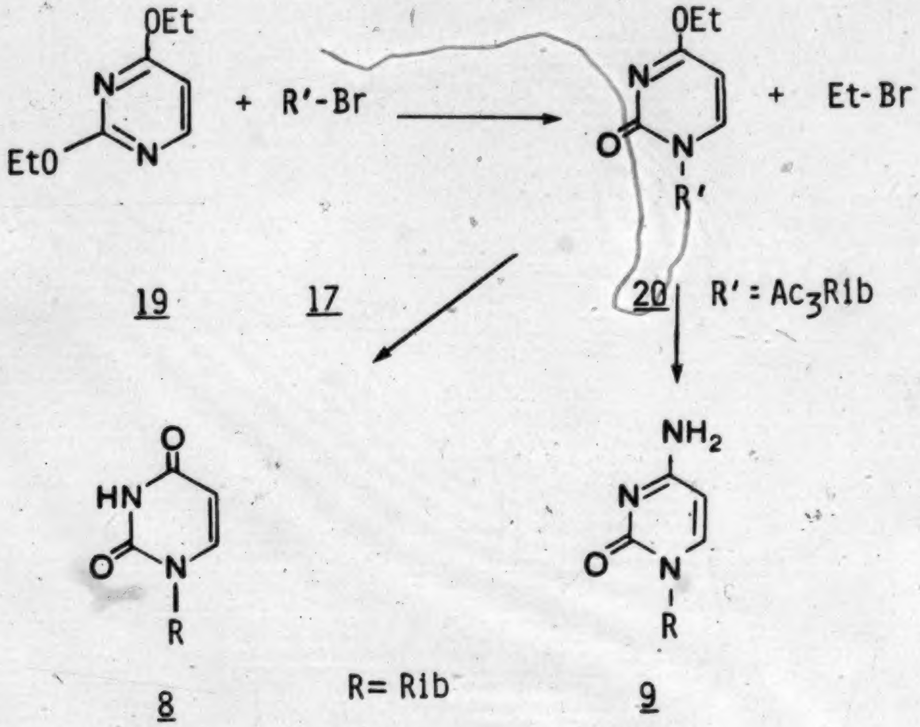
Attempts to condense silver salts of oxopyrimidines with halo-sugar derivatives as described above did not give the expected pyrimidine nucleosides, but rather the O-glycosylpyrimidines.[21] Hilbert and Johnson[22]

SCHEME II

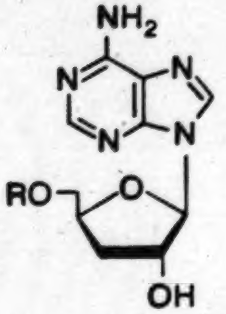


demonstrated that 2,4-dialkoxypyrimidines could be employed as coupling reagents in synthesis of pyrimidine nucleosides. The reaction of tri-O-acetyl-D-ribofuranosyl bromide (17) with 2,4-diethoxypyrimidine (19) provided an intermediate (20) from which both uridine (9)[22] and cytidine (8)[23] were obtained.

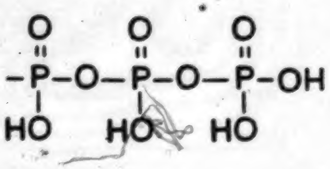
SCHEME III



Until 1948 the nucleic acids were thought to be composed of the four basic nucleoside monomers (6-13) only. The discovery of 5-methylcytosine in a sample of calf thymus DNA by Hotchkiss[24] prompted a surge of reinvestigation. However, it was the isolation of the first nucleoside antibiotic, cordycepin (21), from Cordyceps militaris by Cunningham et al.[25] in 1951 that initiated the boom of chemical research in the nucleoside area. Cordycepin (3'-deoxyadenosine) (21) is a cytotoxic agent which demonstrates a broad spectrum of activity against bacterial strains through the inhibition of purine biosynthesis. The 5'-triphosphate derivative (22) has also been shown to be cytotoxic through the inhibition of nucleic acid biosynthesis.[26]



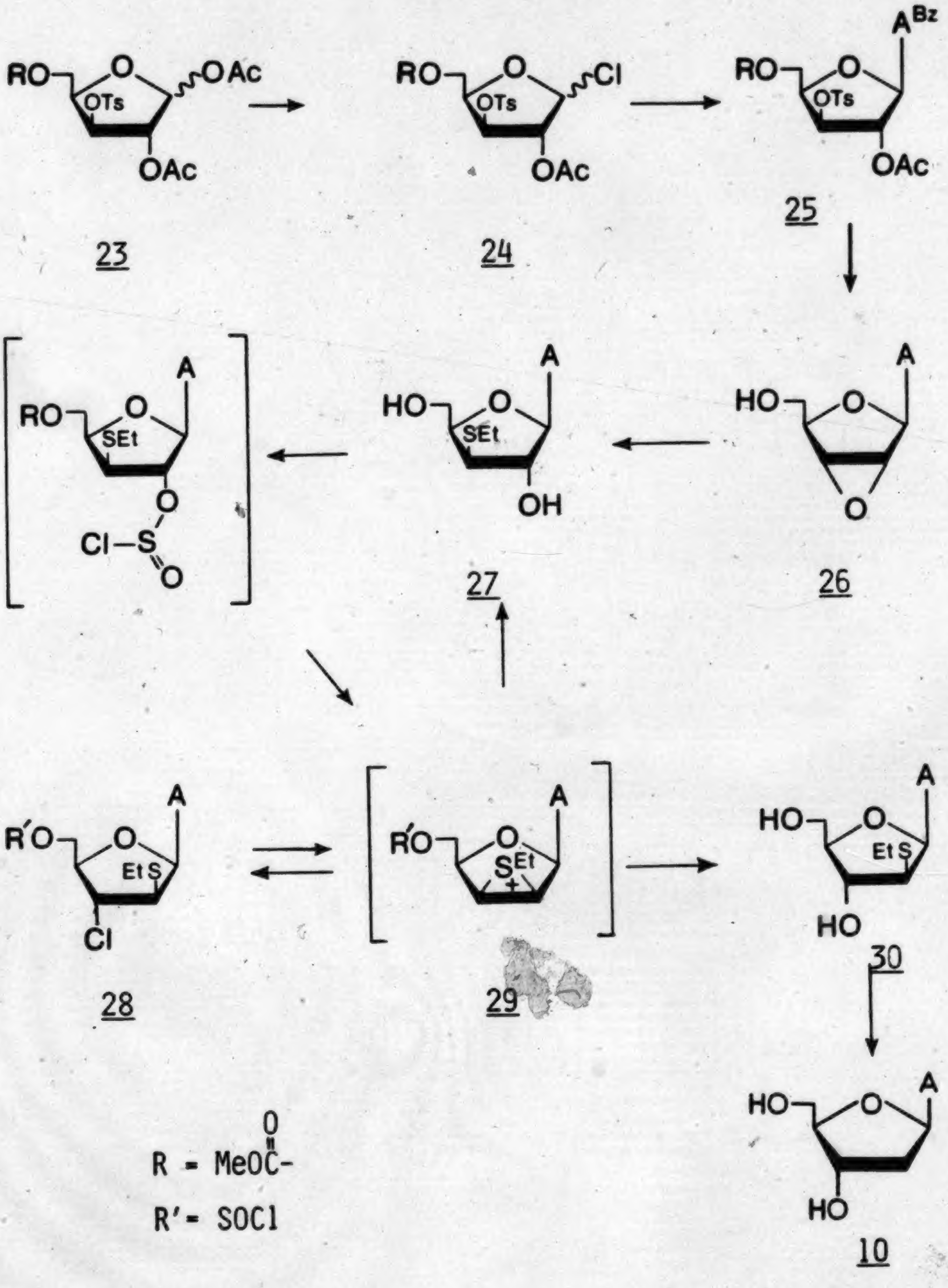
21 R = H

22 R = 

$$-\overset{O}{\overset{\|}{\underset{HO}{\underset{|}{P}}}}-O-\overset{O}{\overset{\|}{\underset{HO}{\underset{|}{P}}}}-O-\overset{O}{\overset{\|}{\underset{HO}{\underset{|}{P}}}}-OH$$

The intense interest generated by the identification of a new class of antibiotics inspired researchers to devise efficient syntheses of potential biologically active compounds from readily obtainable substrates. The employment of chloromercuri derivatives of purines by Davoll and Lowy[27] in place of the silver salts used previously improved yields of coupling reactions significantly. It was later demonstrated[24] that mercuri derivatives of pyrimidines were also effective condensing reagents for the preparation of pyrimidine nucleosides. This led to the first coupling-based synthesis of a 2'-deoxynucleoside, thymidine (13), by Shaw and Warrener[29] in 1958. Baker and co-workers[30] reported the first successful synthesis of 2'-deoxyadenosine in the following year. The starting material used was 1,2-di-O-acetyl-5-*O*-methoxycarbonyl-3-*O*-(*p*-toluenesulfonyl)-*D*-xylofuranose (23) which was converted to the 1-halo derivative (24) prior to condensation with chloromercuri 6-benzamidopurine to give the blocked nucleoside (25). The epoxide (26) was formed upon treatment of (25) with sodium methoxide in methanol. Reaction of (26) with sodium ethylmercaptide afforded the 3'-ethylthio nucleoside (27). Treatment of (27) with thionyl chloride gave the 3'-chloronucleoside (28). Exposure of (28) to aqueous base resulted in a mixture of 2'-(30) and 3'-(27) ethylthio derivatives. A 2',3'-episulfonium ion intermediate (29) was proposed to explain this migration. Desulfurization of (30) gave 2'-deoxyadenosine (10) in a overall yield of 0.5% from (23).

SCHEME IV



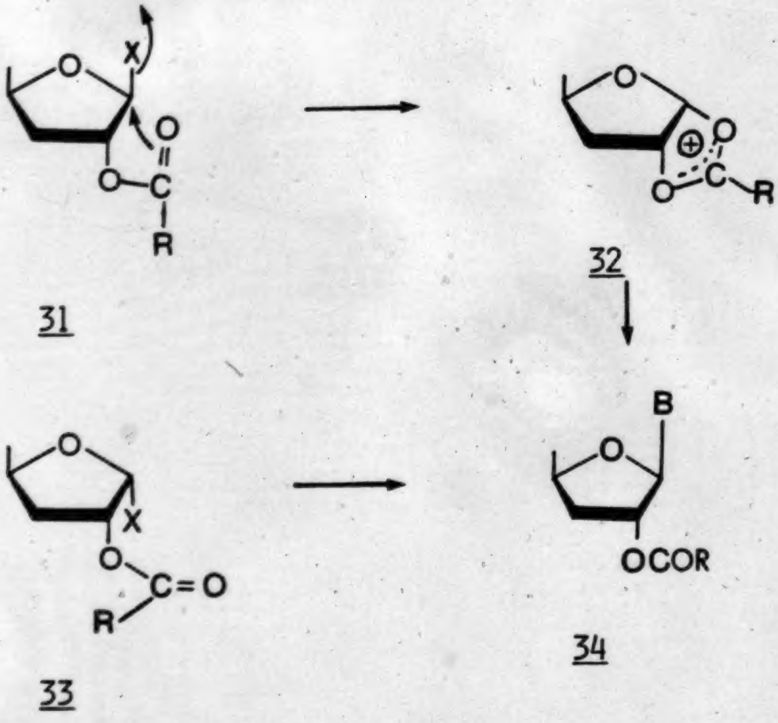
R = MeOC(=O)-

R′= SOCl

The general methods of sugar-base coupling utilized successfully for the synthesis of ribonucleosides have limitations when applied to 2-deoxynucleosides. The di-O-acyl-2-deoxyribofuranosyl chlorides are extremely labile unless stabilized with appropriate blocking groups.[31,32] Anomeric mixtures of the 2'-deoxynucleoside are always obtained in the condensation reactions. The mixtures of anomers obtained in these couplings can be difficult to separate and are much more troublesome if the base component of the nucleoside contains an acidic function. This precludes the use of the Dekker[50] anion exchange chromatography method. Furthermore, the normally unwanted α anomer is frequently an equivalent or predominant product. Numerous reports of base-sugar couplings using various procedures for the synthesis of the naturally occurring 2'-deoxynucleosides and related analogues have appeared in the literature.[31-49]

The stereoselectivity of coupling reactions is dependent on many factors. The method of condensation, choice of solvents, temperature and catalysts can all affect the ratio of anomers obtained. Through mechanistic analysis of reactions involving metal salts of purines, Baker[51] proposed a *trans* rule which postulated that the "condensation of a heavy metal salt of a purine with an acylated glycosyl halide will form a nucleoside with a C-1 to C-2 *trans* configuration." This behavior had been observed in pyrimidine synthesis as well.[52] The experimental facts were rationalized by the intervention of an acyloxonium ion (32) formed by participation of the adjacent *trans* 2-acyloxy group of one anomer (31) of the glycosyl halide. Attack of the heterocyclic base at C-1 of (32) gives the *trans* 1,2-nucleoside (34). Presumably the *cis* anomer (33) can react directly by S_N2 displacement to give the same product (34).

SCHEME V



Sugar substrates which have the necessary participating group at the C-2 position normally give exclusive formation or high ratios of the predicted anomer. Conversely, those substrates which lack this participating C-2 group, such as 2-deoxyglycosyl halides, give rise to anomeric mixtures upon condensation with a base.

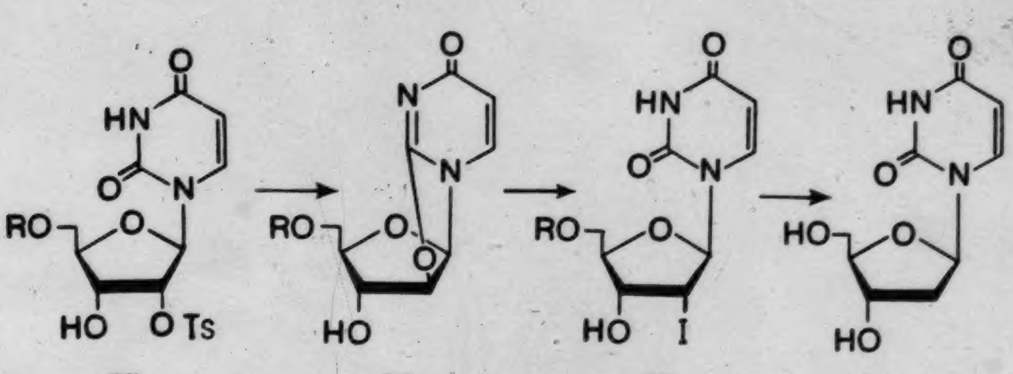
Bardos and co-workers[53] reported that the anomeric ratio of products obtained from reacting pertrimethylsilylated thiopyrimidine bases with 2'-deoxyglycosyl halides could be controlled under certain conditions. By using the purified α anomer of the sugar component and azeotropically removing the trimethylsilyl chloride (TMSCl) as it was produced, excellent yields of a pure β anomer were realized in this silyl Hilbert-Johnson reaction. However, other workers have found that parallel results were not obtained when different bases were coupled.[45]

Ryan, Acton and Goodman[54] have reported the synthesis of 2'-alkylthiopurine nucleosides through a condensation reaction using an alkyl 1-thio-α-D-arabinofuranoside as the sugar precursor. The stereospecificity of the reaction was thought to result from the formation of an episulfonium ion between C-1 and C-2. Trip[55] attempted to extend this result to achieve a fully stereoselective synthesis of β-2'-deoxynucleosides. However the poor yields obtained in the reductive removal of the alkyl-thio group limited the usefulness of this method.

Since ribonucleosides are readily available from natural and synthetic sources as β anomers, they are attractive substrates for 2'-deoxynucleoside synthesis. However, there have been major difficulties involved in obtaining the 2'-deoxynucleosides or suitable precursors such as 2'-halo or 2'-mercapto derivatives. Direct displacement of leaving groups by an external nucleophile at the 2'-position of ribonucleosides is hindered sterically by the base and electronically by the electron deficient C-1' and β oriented base dipole. Furthermore, since the 2'- and 3'-hydroxyl groups are very similar in reactivity, selective functionalization is very difficult. Any intermediate which has both positions "symmetrically" activated will give a predominance of the 3'-derivative from external nucleophilic attack owing to the noted inhibition of reaction at C-2'.

Todd and co-workers[56] were the first to report the synthesis of a pyrimidine 2'-deoxynucleoside from the corresponding ribonucleoside. They found that treatment of 5'-O-acetyl-2'-O-p-toluenesulfonyluridine (35) with sodium iodide gave the 2'-iodo derivative (37) with retention of the *ribo* configuration. Subsequent hydrogenolysis and deacetylation gave 2'-deoxyuridine (38). It was shown that the displacement reaction proceeded via an O-2→2'-anhydropyrimidine intermediate (36). Although Todd obtained an overall yield of less than 10% for this conversion of uridine to 2'-deoxyuridine, the novel method attracted the interest of numerous groups.[57-59]

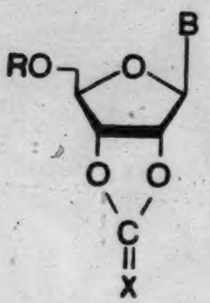
SCHEME VI



35 36 37 38

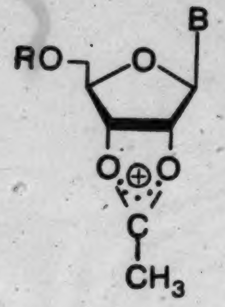
R = Ac Ts = p-toluenesulfonyl

Efficient routes for synthesis of the cyclonucleoside intermediates were developed which utilize the 2',3'-diol structure and hence eliminate the problem of selectively functionalizing two very similar hydroxyl groups. The cyclic 2',3'-O-carbonate (39) and 2',3'-O-thionocarbonate (40) derivatives have been used by several groups[60-64] to give excellent yields of these pyrimidine O-2→2'-cyclonucleosides. The formation of a 2',3'-acetoxonium ion (41), accessible via a variety of procedures, also leads to high yields of the O-2→2'-cyclonucleosides in the pyrimidine series.[65,66] A



39 X = O

40 X = S



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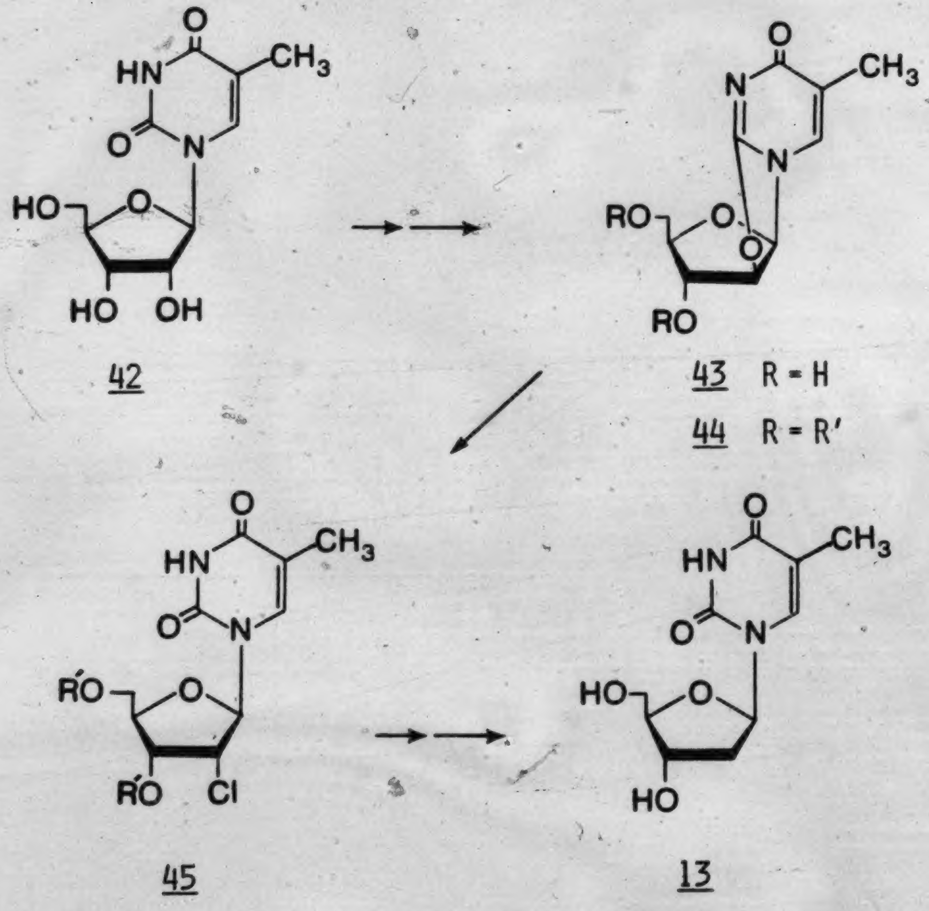
SCHEME VII



R′ = COPh

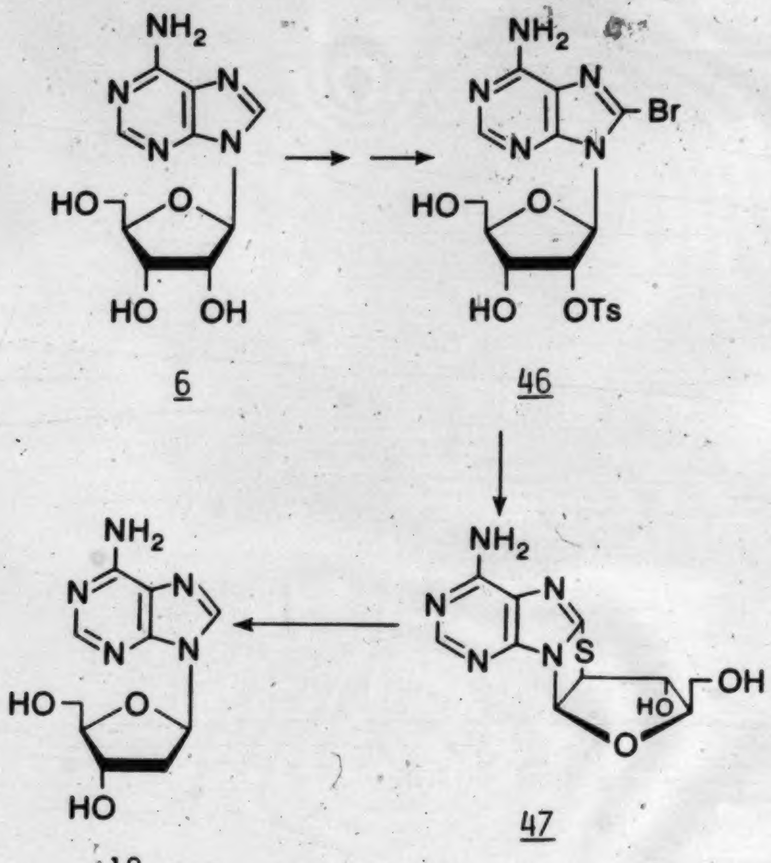
comprehensive review of pyrimidine cyclonucleoside formation has been published recently.[67]

Holý reported a 56% yield of thymidine from 5-methyluridine utilizing the following reaction sequence.[68] The O-2→2'-cyclonucleoside (43), obtained from 5-methyluridine (42) via the cyclic 2',3'-O-carbonate derivative (39) was benzoylated to give the 3',5'-di-O-benzoyl-O-2→2'-cyclo-5-methyluridine (44). Reaction of (44) with dry hydrogen chloride in dimethylformamide gave the 2'-chloro derivative (45). Mild reduction of (44) using tri-n-butylstannane followed by debenzoylation gave thymidine (13).

Attempts to devise efficient syntheses of purine 2'-halo and 2'-deoxynucleosides have proved to be much more difficult. Ikehara and Tada[69] effected purine S-8→2'-cyclonucleoside formation by treatment of the 8-bromo derivative (46) with thiourea. Intramolecular displacement of the tosyl group at C-2' gave the desired product (47).

It was found, however, that Raney nickel desulphurization was very inefficient and low yields of 2'-deoxyadenosine (10) were obtained. Analogous reactions involving 8-oxoadenosine (48) also proved to be disappointing since the C-8-oxy group was extremely difficult to remove.[70]

SCHEME VIII



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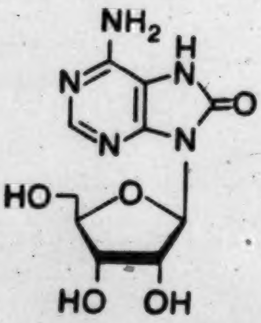
46

47

10



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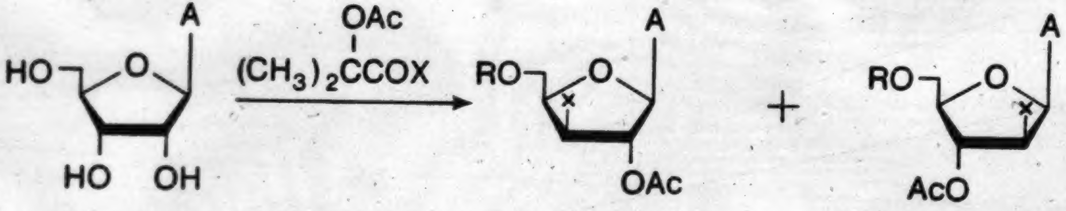
Extensive work on the preparation of purine 2'- and 3'-halonucleosides via 2',3'-acetoxonium ion intermediates (41) has been pursued by both Moffatt and co-workers[71] and Robins and co-workers.[72,73] However, as stated previously, the 2'-halo derivatives (49) are formed as minor products accompanying the predominant 3'-halo derivatives (50). In the case of adenosine, these procedures give ratios of (49) to (50) from approximately 1:9 to 1:6 depending on conditions used.

SCHEME IX

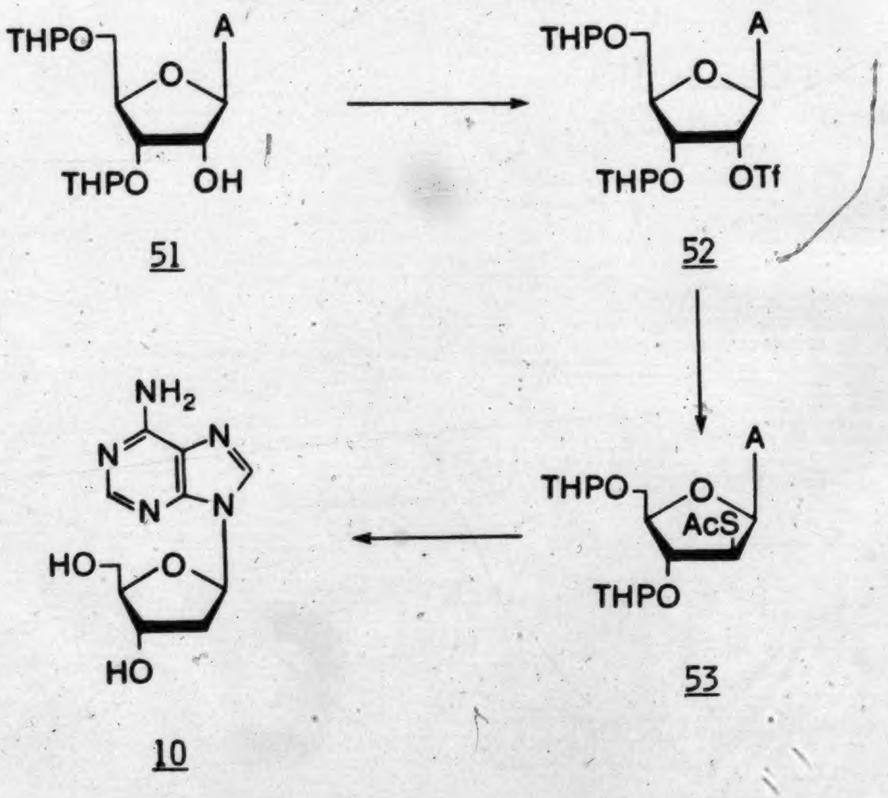


6 50 49

Attempts to synthesize purine 2'-deoxynucleosides through S_N2 displacement have been disappointing. Sporns[74] treated 3'-*O*-methyl-5'-*O*-pivaloyladenosine with 5 equivalents of thionyl chloride in pyridine at 120°C for 1 hour to obtain a 16.5% yield of the 2'-chloro derivative. Ranganathan[75] reported that displacement of the trifluoromethanesulphonyl group was possible at the 2'-position of adenosine. The triflyl derivative

(52) was prepared in 70% yield from the 3',5'-diprotected precursor (51). Reaction with potassium thioacetate at room temperature gave the arabino-thio derivative (53) in 55% yield. Raney nickel desulphurization gave the 2'-deoxyadenosine, although in low overall yield from (51).

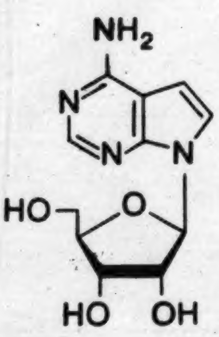
SCHEME X



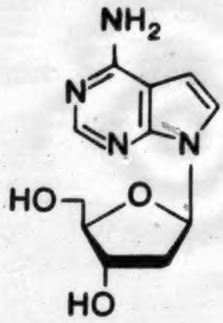
THP = TETRAHYDROPYRANYL

Tf = TRIFLUOROMETHANESULPHONYL

Recently Robins and Muhs[76] reported the first successful conversion of a pyrrolo[2,3-d]pyrimidine nucleoside to its 2'-deoxy analogue. The antibiotic tubercidin (54) was converted to 2'-deoxytubercidin (55) in an eight step procedure that utilized a key episulfonium ion migration analogous to the Baker route to 2'-deoxyadenosine.[30] The 27% overall yield obtained[76] exemplies the difficulty associated with the syntheses of purine-type 2'-deoxynucleosides.



54



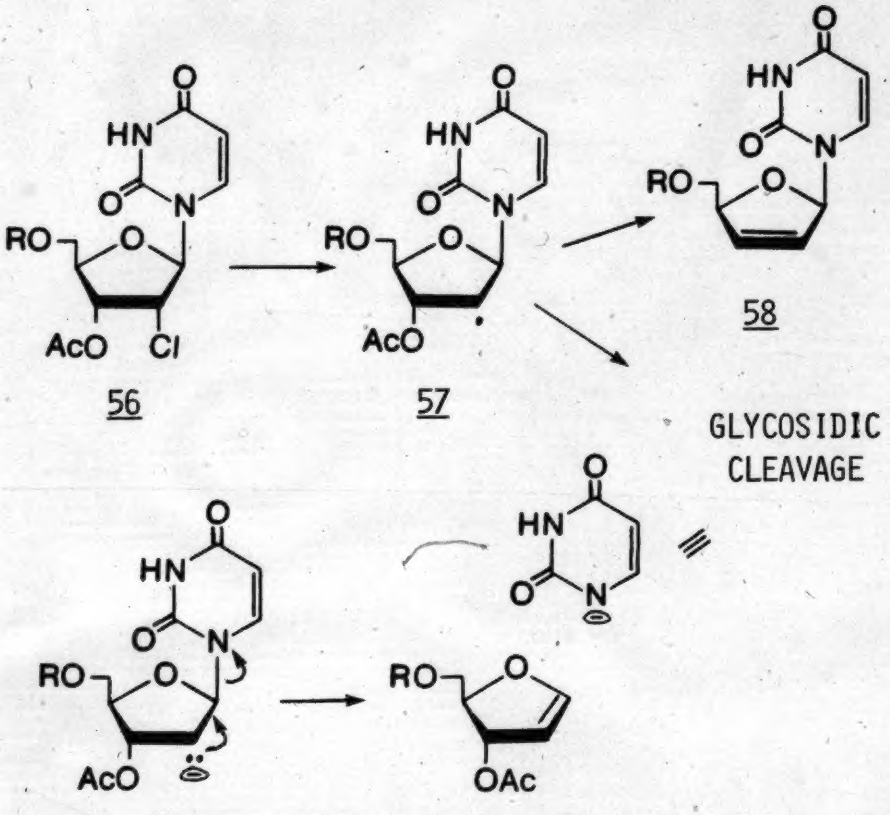
55

B. Recent Developments Pertinent to 2'-Deoxynucleoside Synthesis.

A general and efficient route for preparation of purine 2'-deoxynucleosides has been elusive. The use of S_N2 displacement reactions have been limited due to the intrinsic complications of the molecules as discussed in Chapter I.A. The possibility of utilizing an S_N1 type process is negated since cation formation at C-2' is precluded by the adjacent electron deficient anomeric carbon. However, generation of an anion at C-2' is possible. In studies on the chromous ion induced elimination of vicinal halo acetates, Moffatt and coworkers[77] reported an anomalous result for the *cis*-halo acetate of uridine (56). A large amount of glycosidic cleavage of this normally stable nucleoside was observed upon treatment with chromous acetate.

Moffatt hypothesized that this occurred as a result of the formation of the C-2' radical, (57) which collapsed either to the 2',3'-olefin (58) or with glycosidic cleavage. However, Holý[59] has demonstrated that the free radical mediated reduction of 2'-halouridines with tri-*n*-butylstannane proceeds to the 2'-deoxynucleoside in high yield without glycosyl cleavage. Adachi et al.[78] have studied the electrochemical reduction of (56). They also observed a significant proportion of glycosidic cleavage. The proposed mechanism in this

SCHEME XI



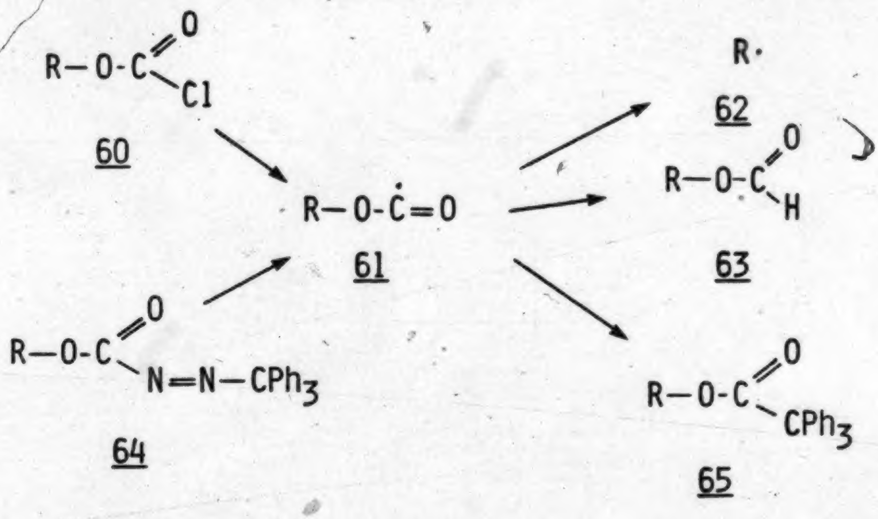
case involves formation of an anion at C-2' (59). Elimination of the base to form the 1'-2' unsaturated sugar provides a plausible explanation. The similarity between these results of Moffatt[77] and Adachi[78] would suggest a common mechanism. This type of elimination of the heterocyclic base was observed also by Robins and Sporns.[79] They found that the generation of an anion at C-2' of an adenosine derivative using the dissolving metal reduction procedure of Ireland and co-workers[80] led exclusively to glycosidic cleavage.

Therefore, homolytic cleavage methods appeared to offer the only feasible approach to efficient deoxygenation of nucleosides at C-2'. This would be consistent with observations that deoxygenation of ribonucleotides to the corresponding DNA components effected by ribonucleotide reductase enzymes in nature are free radical mediated processes.[81]

Photochemical deoxygenations of alcohols (as esters) to alkanes have been investigated by a number of groups recently. Pete and co-workers[82] reported that prolonged ultraviolet irradiation of carboxylic esters in aqueous hexamethylphosphoramide led to good yields of the corresponding alkanes. Application of this method to carbohydrates was successful for the deoxygenation of primary and secondary hydroxyl groups.[83,84] Other derivatives such as sulphonates[85] and thioesters[86,87] have been photochemically reduced to the deoxygenated analogues. However, the strong absorbance of ultraviolet light by the heterocyclic base in nucleosides precludes this approach.

A chemical method was sought that would allow a sufficiently low transition state energy for the homolysis process to overcome the need for high temperatures. The possibility of decarbonation of an alkylcarbonyloxy radical (61) was examined since the generation of carbon dioxide should be energetically favourable. Kuivila and Walsh[88] had reported that such fragmentations did not occur unless the derived alkyl radical (62) was especially stabilized. They found that formates (63) were the major products from reaction of chloroformates (60) with tri-n-butylstannane at 110°C. Beak and Moje[89] obtained a 22% yield of toluene from benzylchloroformate and less than 1% cyclohexane from cyclohexylchloroformate using this method. Barton[90] generated radical (61) through the photolysis of the azo-ester (64), however, only recombination products (65) were observed with no apparent loss of carbon dioxide.

SCHEME XII



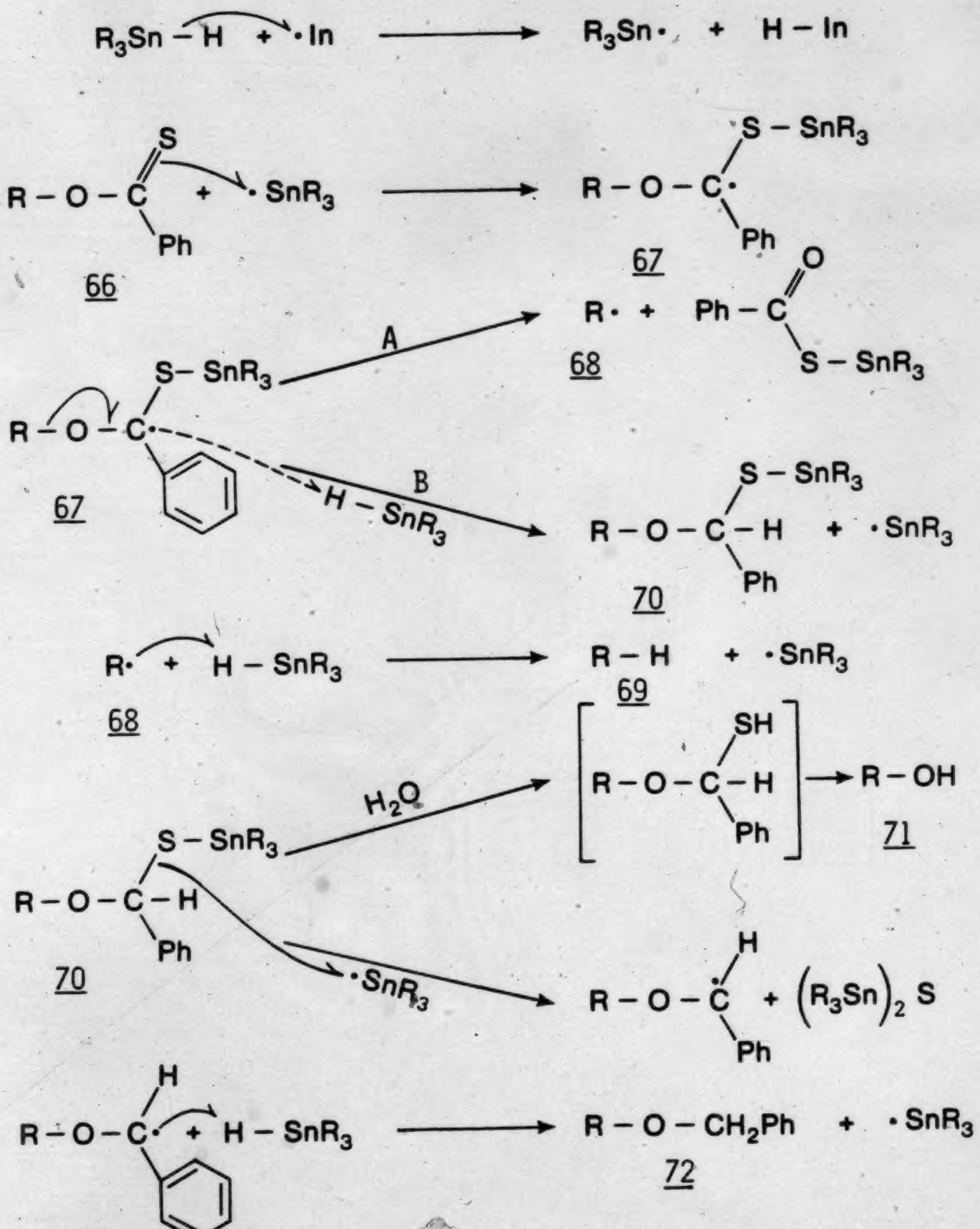
More recently Jackson and co-workers[91] reported that treatment of primary and secondary chloroformates (60) with triisopropylsilane in the presence of a radical initiator at 140°C led to good yields of alkanes. The greater strength of the silicon hydrogen bond (compared to the tin hydrogen bond) makes this reagent less susceptible to hydrogen abstraction by the alkylcarbonyloxy radical (61). The higher temperature employed facilitates the alkyl-oxygen homolysis process. The requirement of higher temperatures, however, precludes application of this method to sensitive substrates.

In 1975, Barton and McCombie[90] reported that thiocarbonyl esters of secondary alcohols (66) underwent homolytic cleavage upon treatment with tri-n-butylstannane to give the deoxygenation product.

The proposed mechanism, illustrated in Scheme XIII, involved attack of the tri-n-butylstannyl radical on sulphur of (66) to form a stabilized radical intermediate (67). The radical could react by two pathways: Homolysis of the alkyl-oxygen bond would form the thermodynamically stable carbonyl group and is designated as pathway A. Hydrogen capture by the newly formed alkyl radical (68) would lead to the deoxygenated product (69). The driving force for the reaction was postulated to arise from the greater stability of the carbonyl over the thiocarbonyl function; hydrogen capture would form (70) via pathway B. Subsequent hydrolytic processing of (70) would lead to the starting alcohol (71). The isolation of benzyl ether products (72) from treatment of thionobenzoate esters with tri-n-butylstannane presumably arises from the dethiation of (70) followed by a second hydrogen capture.[92]

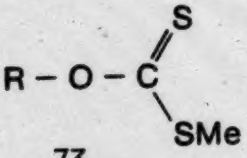
The energy difference between the two mechanistic

SCHEME XIII

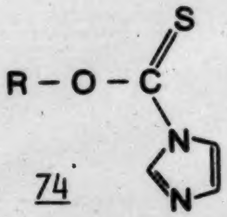

R3Sn – H + •In → R3Sn• + H – In
66
67
A
B
68
70
69
H2O
71
72
R – OH
R – H + •SnR3
R – O – CH2Ph + •SnR3
(R3Sn)2 S

pathways A and B is apparently quite small. Hence, the proportion of deoxygenation product is dependent on the relative stabilities of intermediate (67) and the alkyl radical (68) generated by its homolysis. Primary alcohol derivatives reacted exclusively via pathway B due to the relative instability of a primary alkyl radical. Barton found that pathway A was favoured over pathway B for secondary alcohol thionoesters at higher temperatures. High dilution, whereby immediate hydrogen capture by intermediate (67) was less likely, also favoured pathway A.

Other thiocarbonyl derivatives examined by Barton[90] showed similar reactivity towards tri-n-butylstannane and also lead to deoxygenation products. Ring substituted thionobenzoates showed little advantage over the parent derivative. However, the methyldithiocarbonate (methylxanthate) group (73) eliminated the possibility of benzyl ether formation. Deoxygenation yields reported for all these derivatives were from 70-85% using steroid and simple carbohydrates as model compounds. Thioimidazolide derivatives (74) also were deoxygenated. They were



73

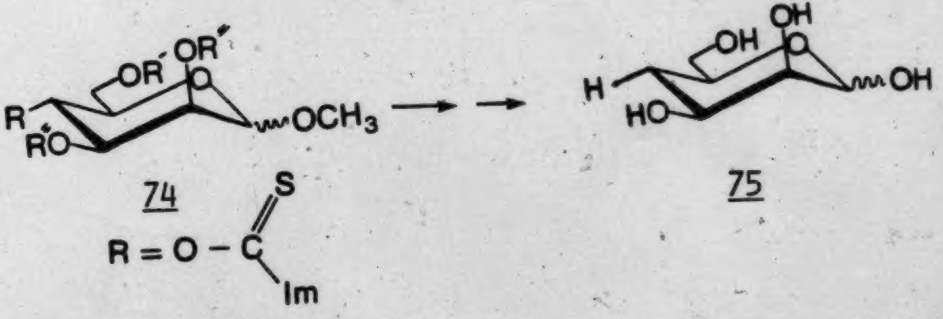


74

synthesized easily under relatively mild conditions. Barton noted, however, that the thioimidazolide reductions were less consistent and were dependent on the substrate used. He attributed this behavior to the formation of imidazole in the reaction. The decomposition of tri-n-butylstannane to hexa-n-butyldistannane is a process catalyzed by the presence of secondary amines.[93]

Applications of Barton's methods to more demanding synthetic problems have met with varied success. In the total synthesis of hirsutene, Tatsuta and co-workers[94] prepared the dithiocarbonate derivative of a hirsutene precursor and reported a 90% conversion to the deoxygenated product upon treatment with tri-n-butylstannane. Rasmussen[95] recently reported that an 87% yield of a 4-deoxypyranoside (75) was obtained via reduction of the thioimidazolide derivative (74).

SCHEME XIV



74

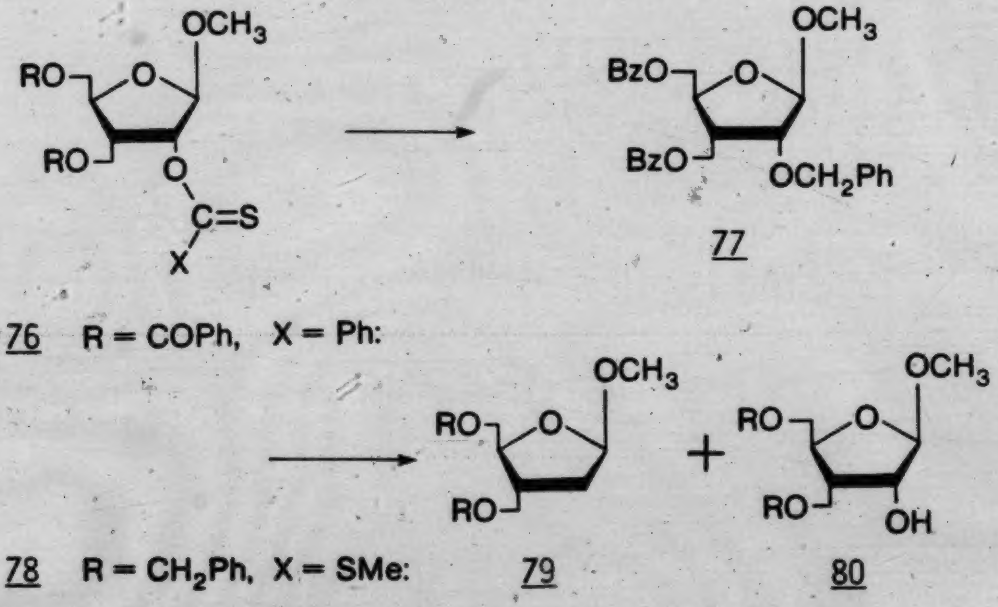
75

R′ = COPh

R″ = >C(CH$_3$)$_2$

Acton et al.[92] found that the 2-thionobenzoate derivative of 5-O-benzoyl-3-deoxy-3-C-[(benzoyloxy)methyl]-1-O-methyl-β-D-allofuranose (76) gave predominant formation of the corresponding benzyl ether (77) upon reduction. Brimacombe et al.[96] noted similarly poor results using this method. Unpublished results from our laboratories also have confirmed that benzyl ether formation is a consistent problem in this reaction. Acton's group reported that reduction of the methyldithiocarbonate derivative of the dibenzylated analogue of (78) gave a 2:1 ratio of deoxygenated product (79) to starting alcohol (80).

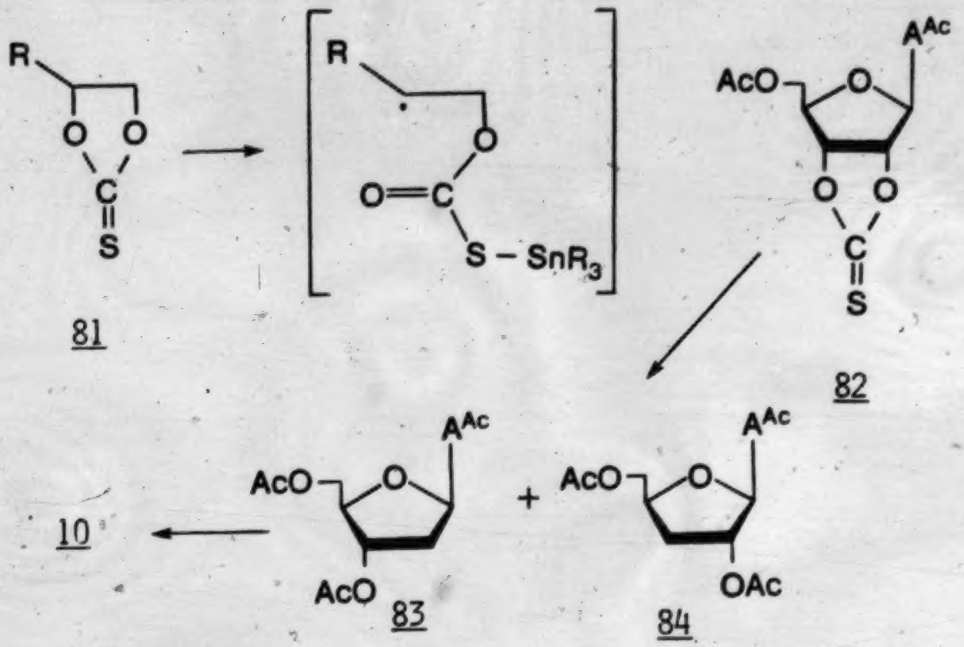
SCHEME XV



In addition to the dual reaction pathways, there are limitations of Barton's method arising from the preparation of the thionocarbonate derivatives. The strongly basic conditions used for the introduction of thiobenzoyl and methyldithiocarbonate groups are incompatible with several useful blocking groups employed in carbohydrate and nucleoside chemistry. An alternative synthesis of thionobenzoates was reported by Barton.[90] However, it involves the inconvenient generation and use of imidoyl chlorides and hydrogen sulfide.[90] As well, these thionobenzoate derivatives are the most prone to give high ratios of by-products relative to deoxygenation.

Barton[97] also examined the reduction of cyclic thionocarbonates (81) with tri-*n*-butylstannane. It was found that homolytic opening of cyclic thionocarbonate formed from one primary and one secondary hydroxyl group gave the alkane arising from secondary radical formation exclusively. The more stable radical and resulting alkane was generated. This method was applied to the 2',3'-cyclic thionocarbonate of 6-*N*,5'-*O*-diacetyladenosine (82), obtained in 46% yield by the procedure of Goodman and co-workers.[98] Treatment of a solution of (82) in dimethylacetamide with tri-*n*-butylstannane at 175°C was followed by basic hydrolysis and acetylation. The product mixture was found to contain 60% of the 2'-deoxy (83) and 29% of the 3'-deoxy (84) derivatives. Isolation and removal of the acetyl groups gave 2'-deoxyadenosine

SCHEME XVI

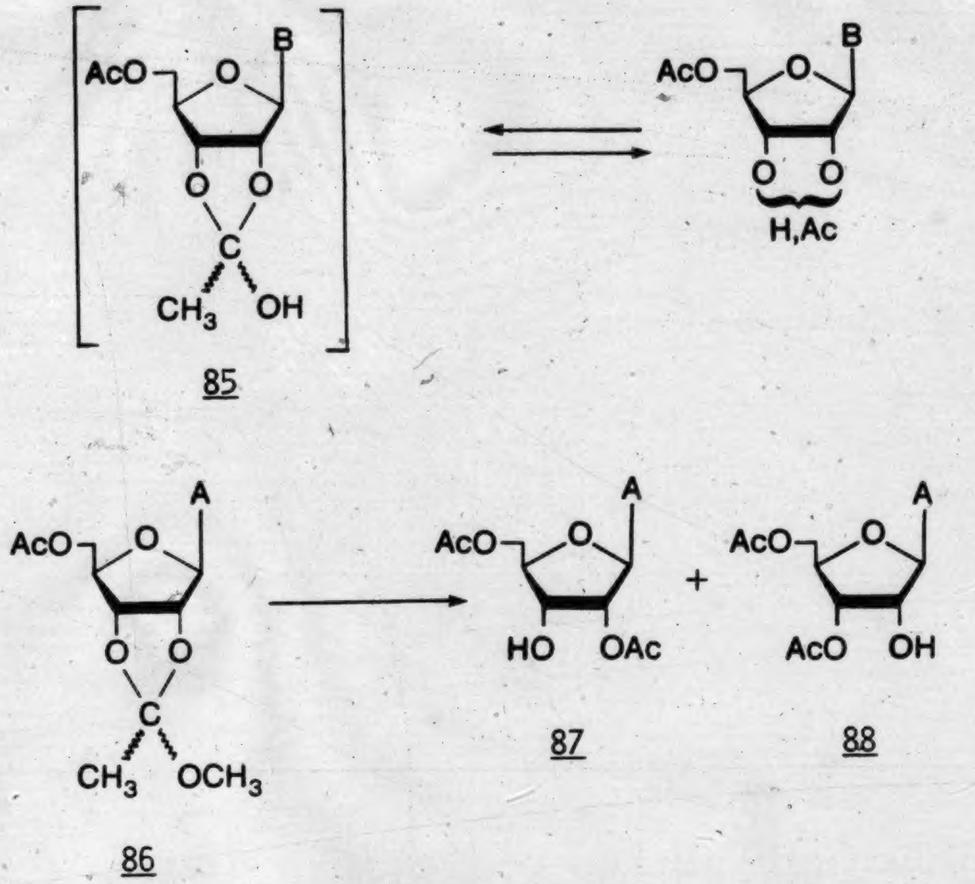


(10) in ~22% overall yield from adenosine (6). This yield is comparable to other methods of 2'-deoxyadenosine synthesis discussed in Chapter I.A.[69,71-73,75] Differing ratios of 2'- and 3'-deoxynucleosides would be expected upon application of this route to other substrates. The promise of this approach is limited by the low overall yield obtained and required separation of isomers.

Thus, a general method of 2'-deoxygenation was lacking although significant progress toward solving the problem had been made primarily by the work of Barton and his co-workers.

A very serious obstacle encountered in the quest for a general 2'-deoxygenation procedure was the lack of a method for the selective 3',5' protection of the trihydroxy nucleosides. A variety of methods exist by which primary alcohols may be derivatized in the presence of secondary hydroxyl groups.[99] Hence the 5'-hydroxyl group can be protected selectively with no difficulty. The problem lay in differentiating between the 2'- and 3'-hydroxyl functions. Since both secondary groups are very similar in terms of reactivity and steric environment, methods which involve partial rather than total derivatization of the hydroxyl groups give mixtures of 2',5' and 3',5' isomers.[100-102] Although resolution of these mixtures is usually possible by chromatographic means, the overall yield of 3',5' blocked nucleoside is normally well below 50%. Monoester derivatives of this cis-glycol system undergo rapid migration under slightly basic conditions.[102-104] This process, illustrated in Scheme XVII for the case of the acetyl function, involves a cyclic orthoester intermediate (85) and gives rise to an equilibrium mixture of products. Reese and Sulston[105] reported that 5'-O-acetyl-2',3'-O-methoxyethylidene-adenosine (86) could be opened under mildly acidic conditions to give a mixture of 2',5' (87) and 3',5'-di-O-acetyladenosine (88). The 3',5' isomer (88) could

SCHEME XVII



85

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87

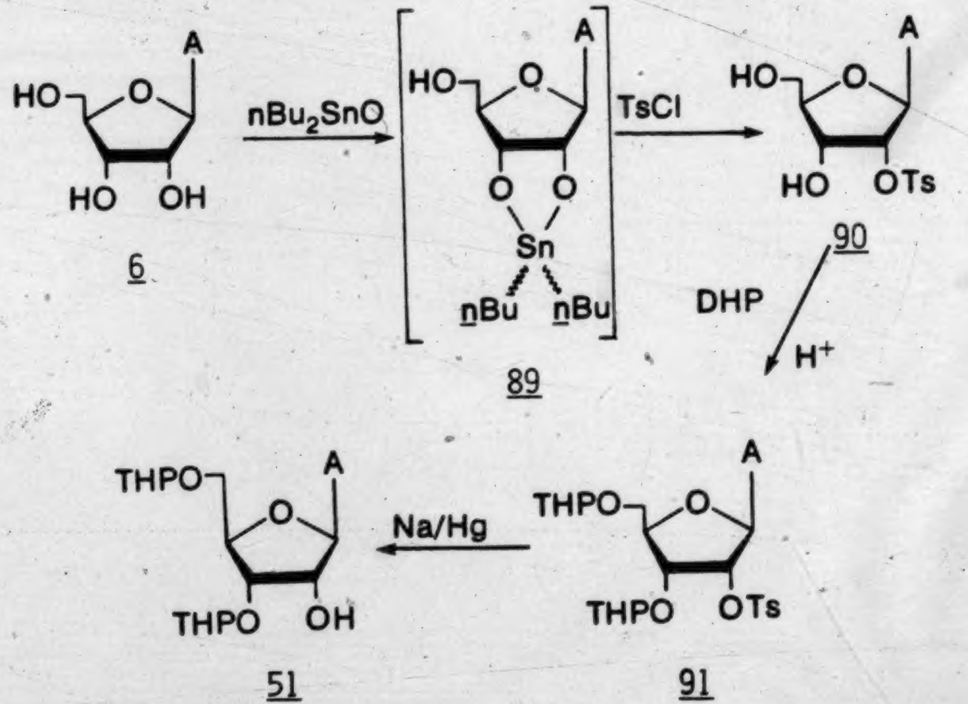
88

be crystallized from solution, which shifted the equilibrium to favour this isomer. Good yields of crystalline (88) were realized. However, re-equilibration proceeds upon dissolution in solvents required for derivatization of the 2'-hydroxyl group.

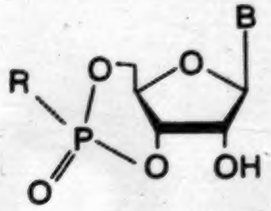
Moffatt and co-workers[106] reported high yields of

2'-O-tosyladenosine (90) from adenosine (6) via *in situ* generation of an activated stannyl acetal (ketal) intermediate (89). Ranganathan[75] prepared 3',5'-di-O-tetrahydropyranyl-2'-O-tosyladenosine (91) from 2'-O-tosyladenosine (90). Treatment of (91) with sodium amalgam gave 3',5'-di-O-tetrahydropyranyladenosine (51) in 45% yield from adenosine.

SCHEME XVIII



Nucleoside cyclic 3',5'-monophosphates (92) have been used occasionally as selectively blocked substrates.[107] However, the acidically ionized phosphate function is not amenable to use in most organic solvents. Preliminary investigations into the utilization of cyclic phosphate triesters (93) and cyclic phosphonates (94) did not appear to be promising.[108] The possibility of developing a selective carbocyclic protecting group was pursued briefly in our laboratory.

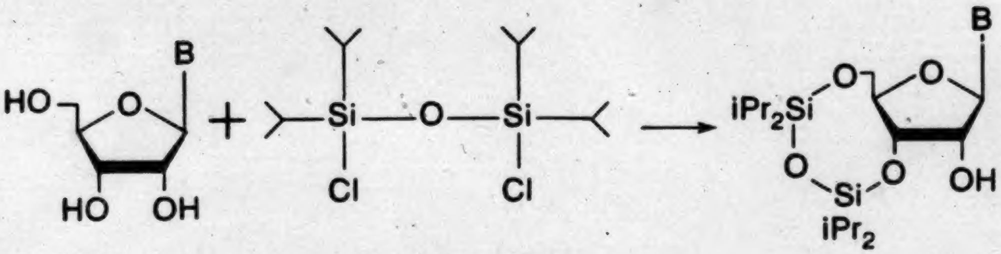


92 R = OH
93 R = O-Alkyl
94 R = Alkyl

In 1978, Markiewicz and Wiewiorowski[109] reported a reagent for the selective preparation of 3',5' protected nucleosides. They had observed that triisopropylsilyl chloride reacted with primary alcohols 10^3 times faster than with secondary alcohols. When 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (95) was allowed to react with uridine in the presence of imidazole, 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridine (96) was obtained in 70-80% yield. The analogous adenosine derivative (97) also was produced in comparable yield.

The disiloxyl group was removed smoothly using a soluble fluoride ion salt, but was relatively stable to mild acidic and basic conditions.

SCHEME XIX



95

96 B = U

97 B = Ad

This realization of an efficient and facile means to selectively protect nucleosides at 0-3' and 0-5' was essential to the development of a general 2'-deoxygenation procedure.

These findings of Markiewicz have been substantiated in our laboratory and a representative variety of 3',5'-tetraisopropyldisiloxyl nucleosides have been prepared in high to quantitative conversion yields.

The ^{1}H NMR spectra of all of the 3',5' blocked nucleoside derivatives were very similar. The anomeric proton coupling constant was small in all cases. This indicated that a relatively fixed sugar conformation existed in these compounds. It previously had been determined by ^{1}H NMR analysis in our laboratories that all of the nucleoside 3',5'-cyclic monophosphate derivatives exist in consistently rigid conformations that could be utilized to distinguish between α and β anomers of the precursor nucleosides.[110] Difficulties involved in preparing those derivatives, however, have severely limited practical application of this unequivocal method of anomeric determination.

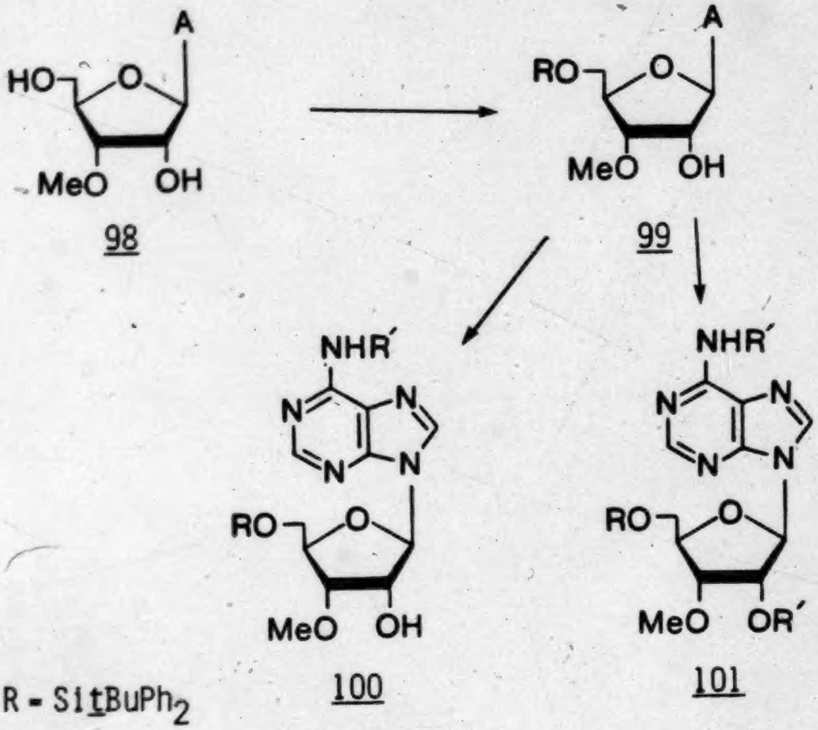
Similarities and consistency of the ^{1}H NMR spectra of the nucleoside 3',5'-cyclic monophosphate and 3',5'-tetraisopropyldisiloxyl compounds suggested that the latter easily prepared derivatives might be useful for this anomeric configuration determination. A high field ^{1}H NMR and single crystal X-ray structure determination was pursued in order to evaluate this possibility.

RESULTS AND DISCUSSION

A. A General Procedure for the Conversion of Ribonucleosides to 2'-Deoxynucleosides.

In 1975, Barton and McCombie[90] reported that secondary alcohols could be reductively deoxygenated through the homolytic cleavage of thionoester derivatives. This method was discussed at length in Chapter I.B. We examined the applicability of this novel approach to the problem of 2'-deoxygenation in purine nucleosides. The model compound chosen for our investigation was 3'-O-methyladenosine (98). A facile methylation procedure using diazomethane and stannous chloride had been developed in these laboratories which gave mixtures of 2'-and 3'-monomethylated nucleosides.[111] Use of the 3'-O-methyl compound eliminated the problem of selective blocking of the 2',3' diol system. The 3'-O-methyl group was expected to exert minimal steric and electronic interference at the 2' hydroxyl function and thus would allow clear evaluation of the deoxygenation method. The primary 5'-hydroxyl function was blocked selectively with the tert-butyldiphenylsilyl group[112] to give the 3' and 5' protected nucleoside (99). This silyl protecting group can be removed easily with fluoride anion[113] but is stable to mild acid and base conditions. Furthermore its nonpolar and bulky substituents serve to increase the lypophilicity of the nucleoside.

SCHEME XX

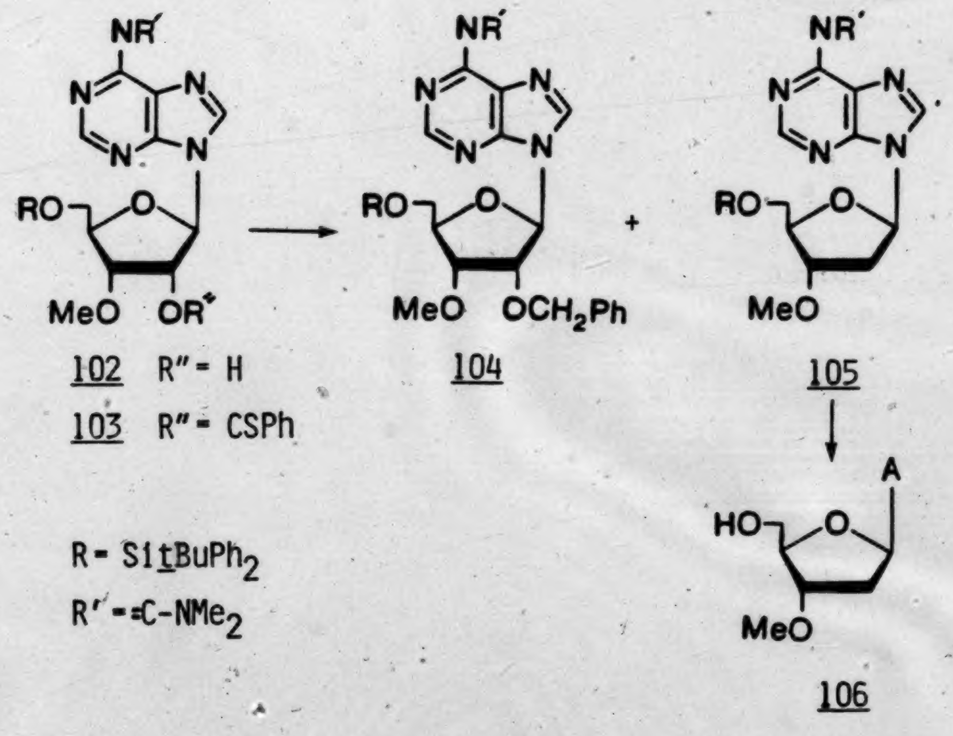


R = Si*t*BuPh$_2$

R′ = CSPh

When (99) was treated with thiobenzoylimidazolide under the strongly basic conditions of the Barton procedure,[114] two products were obtained. The major component was found to be the 6-N-thiobenzoylated derivative (100) and the minor compound the 6-N,2'-O-dithiobenzoylated nucleoside (101). Hence the 6-amino group on the base was protected prior to thiobenzoylation. Treatment of (99) with dimethylformamide dimethylacetal in dimethylformamide[115] gave the 6-N-dimethylaminomethylene derivative (102). This N-6 blocking group is difficult to remove selectively since conversion to the 6-N-formyl product occurs on exposure to acid. Subsequent basic conditions are required to regenerate the free 6-amino function. However, few methods exist for selective protection of a relatively unreactive amino group with a base stable protecting group in the presence of a free hydroxyl function. When (102) was subjected to the previously noted thiobenzoylimidazolide procedure, the 2'-O-thionobenzoyl nucleoside (103) was obtained in 64% yield.

SCHEME XXI



Slow addition of a dilute solution of (103) in toluene to a refluxing solution of tri-n-butylstannane in toluene resulted in the formation of two major products. These were identified as the 2'-O-benzyl ether (104) and the 2'-deoxy derivative (105). The viability of this deoxygenation process was verified by isolation of 2'-deoxy-3'-O-methyladenosine (106) after treatment of (105) with tetra-n-butylammonium fluoride (TBAF) followed by acidic workup and anion exchange chromatography on Dowex 1 X 2 (OH^-).[50] However, it should be noted that (104) was a major product of the reaction. Barton[90] reported that the yield of deoxygenated product increased as the concentration of the reacting species decreased. In our reductions of nucleoside derivatives, benzyl ether formation always occurred to a large extent irrespective of changes in addition procedures, concentrations and temperatures.

Methyldithiocarbonate (methylxanthate) derivatives were also reported to give deoxygenated products upon treatment with tri-n-butylstannane.[90] When (99) was dissolved in THF and treated with two equivalents of sodium hydride, excess carbon disulphide and methyl iodide according to the Barton procedure,[90] multiple product formation was observed by TLC. Similarly, reaction of (102) under these conditions resulted in a mixture of compounds.

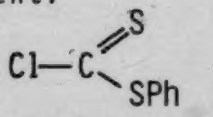
Although no single compound was isolated for characterization, purine methylation at N-1 and Dimroth rearrangement to the 6-N-methyl products are known to occur under similar conditions.[116] In view of the complex mixtures obtained by this procedure, this approach was abandoned.

Thus Barton's methods of deoxygenation, while conveniently successful with steroids and simple carbohydrate derivatives, were not directly applicable to nucleosides. The forcing basic conditions used to generate the thiocarbonyl derivatives were not selective and required fully protected substrates. Although the 3'-O-methyl ether and 6-N-dimethylaminomethylene groups could be used in model studies, the difficulties associated with removal of these functions precluded their use as protecting groups. Furthermore, the low yield of 2'-deoxygenated product obtained from the reduction of the thionobenzoate was unsatisfactory.

The problem of 2'-deoxygenation of nucleosides was separated into two interdependent studies. The first concern was to find an alcohol derivative which would undergo efficient alkyl-oxygen homolysis and could be synthesized under mild conditions. The second was to establish a procedure for the appropriate selective 3' and 5' protection of nucleosides. The protecting group(s) must be able to withstand the conditions required for the above derivatization and homolysis at C-2' but must be subject to removal under relatively mild conditions after the reduction step. Since purine 2'-deoxynucleosides are very susceptible to acid hydrolysis, blocking groups that require acidic conditions for removal were excluded.

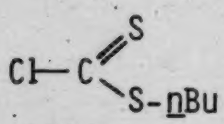
A reagent for activation and removal of the 2'-oxygen atom was desired that would functionalize alcohols under normal acylation conditions. Originally we examined the possibility of using thiobenzoyl chloride. Dithiobenzoic acid was prepared according to the procedure of Houben[117] through the reaction of phenylmagnesium bromide with carbon disulphide. The magenta colored ethereal solution obtained was very unstable toward air. Reaction of this product with thionyl chloride gave a complex mixture which did not yield the desired thiobenzoyl chloride. Dithiobenzoic acid was stabilized through salt formation (Zn, Pb). However, regeneration of the free acid was required prior to reaction with thionyl chloride. The extreme sensitivity of dithiobenzoic acid and thiobenzoyl chloride to oxygen and/or water was a serious limitation and hence this reagent was abandoned.

A chlorodithiocarbonate derivative appeared to offer more potential as an acylating reagent owing to increased stability and ease of preparation. Phenyl chlorodithiocarbonate[118] (107) and *n*-butyl chlorodithiocarbonate[119] (108) were prepared by treatment of thiophosgene with the appropriate thiol. Both were stable distilled liquids. Cholesterol (109) was chosen as a simple model secondary alcohol. When dried cholesterol was dissolved in pyridine and treated with (107) or (108) at room temperature the solution gradually became coloured and acylation was very slow. The addition of 4-*N*,*N*-dimethylaminopyridine (DMAP), a base demonstrated to be a powerful acylation catalyst,[120] made no observed difference. It was necessary to perform the reaction at 45°C for a shorter time to achieve optimum product formation. The 3-phenylxanthate (110) and 3-*n*-butylxanthate (111) derivatives of cholesterol were obtained in ~80% yields through multiple addition of the appropriate reagent.



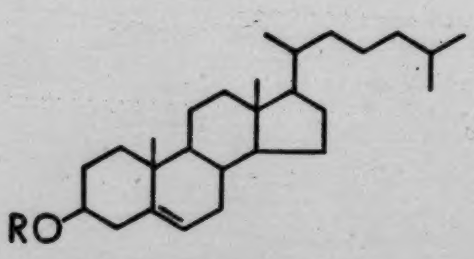
$\mathrm{Cl{-}C({=}S){-}SPh}$

107



$\mathrm{Cl{-}C({=}S){-}S{-}}n\mathrm{Bu}$

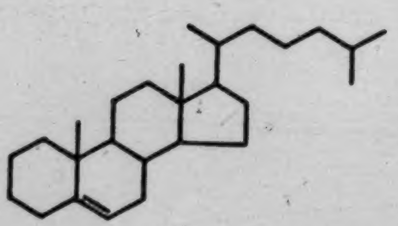
108



109 R = H

110 R = CS_2Ph

111 R = CS_2*n*Bu

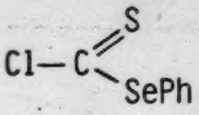


112

Treatment of (110) or (111) with tri-n-butylstannane in refluxing toluene, according to the procedure of Barton[90] gave cholestene (112) in 75-80% yield. A minor but significant amount (10-15%) of cholesterol (109) was obtained also. No reaction was observed when these reductions were attempted in refluxing benzene. However, addition of the free radical initiator 2,2'-azobis-(2-methylpropanitrile) (more commonly referred to as azobisisobutyronitrile (AIBN)) to the benzene solution resulted in cholestene formation at 80°C without concomitant formation of cholesterol. Furthermore, it was found that product formation was unaffected by the concentrations of substrate and tri-n-butylstannane under these conditions. It had been noted by Barton that without initiator present the yields of reduced products were inversely proportional to the concentrations of reactants.[90]

Phenylselenylthiocarbonyl chloride (113) and phenyl chlorothionocarbonate (114) also were examined as acylating reagents. Treatment of diphenyldiselenide with sodium borohydride in ethanol[121] followed by introduction of thiophosgene gave (113) in low yield. The orange-red liquid was distilled prior to use. This reagent (113) solidified on contact with pyridine. Treatment of cholesterol with (113) in pyridine gave no observed formation of product. Variation of reaction temperatures and solvents had little effect and this approach was abandoned.

The procedure of Miyazaki[122] was employed for the preparation of (114) from phenol and thiophosgene. The resulting yellow liquid was stable and was purified in good yield by vacuum distillation.



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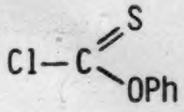
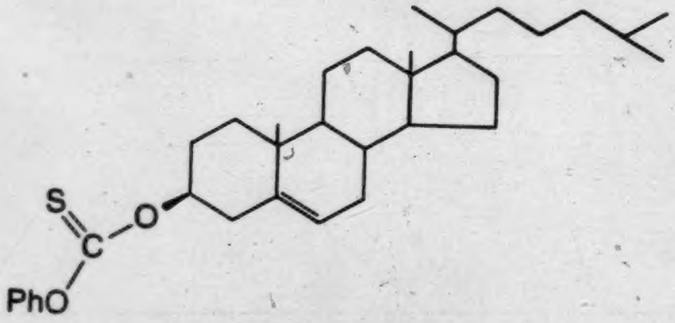


114

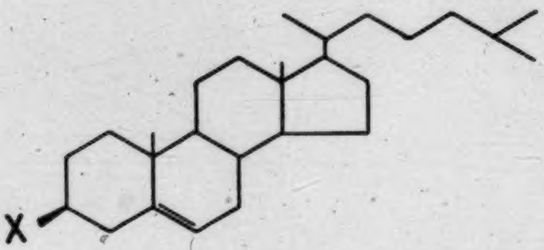


115

When a solution of cholesterol in pyridine was treated with (114) at room temperature moderate conversion to the phenylthionocarbonate derivative (115) was observed. The reaction solution became coloured more slowly than the analogous reactions with the chlorodithiocarbonate reagents (107) and (108). Acylation was possible at room temperature as opposed to 45°C. A 96%

yield of (115) was obtained when the reaction was performed at room temperature in dichloromethane using 3-4 equivalents of pyridine. Thus, in terms of acylating potential, (114) was superior to other derivatives examined. Treatment of (115) with tri-*n*-butylstannane in refluxing toluene without an initiator resulted in almost no reaction occurring. Repeating this treatment of (115) at 80°C in the presence of AIBN resulted in a product distribution indistinguishable from that of the xanthates (110) and (111) under identical conditions. In all three cases cholestene was the major product. However, a steroidal by-product was formed also. The mass spectrum of this by-product showed a molecular ion of m/z 401 which is indicative of the presence of a nitrogen atom. The base peak at m/z 368 (arising from the formation of $\Delta^{3,5}$ cholestadiene) was common to all the cholesterol derivatives with a labile group at C-3. We speculated that this by-product could result from reaction of the steroidal radical formed and AIBN. When the reductions of (110), (111) or (115) were performed in refluxing toluene using di-*tert*-butylperoxide as the initiator, cholestene was the sole product. A near quantitative conversion to cholestene was indicated by TLC and an 84% isolated yield was obtained after chromatography on alumina followed by crystallization.

We evaluated reactions of (110), (115) and 3β-



109 X = OH

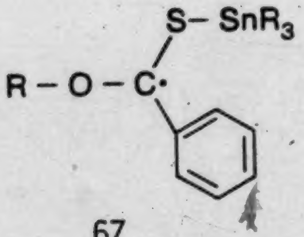
110 X = OCS_2Ph

116 X = OCSPh

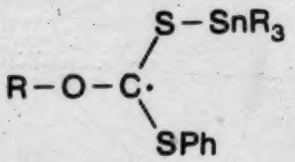
112 X = H

115 X = OCS(OPh)

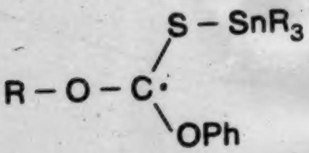
117 X = OCH_2Ph



67



118



119

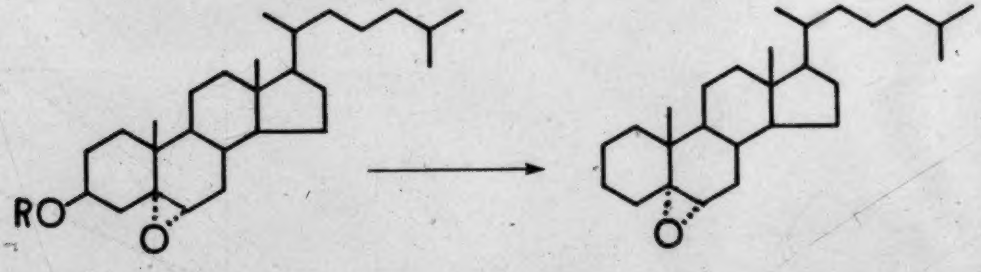
cholesterylthionobenzoate[90] (116) with tri-n-butylstannane under different conditions in an attempt to arrive at a plausible explanation for the differences observed. As discussed in Chapter I.B., Barton found that product to by-product ratios in the reduction of thionobenzoates were very sensitive to reactant concentrations. In our studies on (116) we also found this to be true. Treatment of (116) with tri-n-butylstannane in refluxing benzene with or without added AIBN gave the 3-benzyl ether derivative (117) and cholesterol (109) as the respective major and minor products. When the reaction was conducted in refluxing toluene, equal amounts of (117) and cholestene (112) were obtained as well as a minor amount of (109). Slow addition of the reactants to toluene at 110°C gave (112) as the major product. However, minor quantities of (117) and (109) were always formed. The postulated intermediate benzylic radical (67) would also be stabilized by the α-sulphur substituent. Owing to this stabilization, the lifetime of (67) might permit bimolecular hydrogen transfer from the stannane to compete with the desired unimolecular carbon-oxygen homolysis (β scission). This prediction is consistent with the finding that at 80°C the benzyl ether (117) which results from hydrogen transfer is the major product observed. Barton's observations that high dilution and higher temperatures favoured deoxygenation[90] also are consistent with the intermediacy of (67).

Reaction of the phenyldithiocarbonate (110) with tri-*n*-butylstannane in the absence of a free radical initiator proceeds at 110°C but not at 80°C. Thus it would appear that the activation energy for initiation of reaction of these derivatives is higher than that of the thionobenzoates. The α-dithio radical intermediate (118) would be presumed to be less stabilized than the benzylic thio radical (67). The formation of by-product cholesterol in the uninitiated reaction of dithiocarbonate (110) with stannane at 110°C was assumed to arise from hydrogen transfer to (118) in an analogous manner to that occurring with (67). However, the observations that the reaction is independent of concentration and proceeds at a lower temperature in the presence of AIBN mitigate against this pathway as the sole route for formation of cholesterol. It might be more plausible to suggest that formation of the alcohol proceeds independently from the pathway for the alkane. These processes might not share (or else might diverge in early pathways from) the same initiation intermediate. The involvement of an intermediate such as (118) was not substantiated. A more detailed study of all the products formed in the reaction would be required for a more defined mechanistic analysis. Since the mechanistic implications of cholesterol formation were of interest to us for practical considerations only, a more detailed study for theoretical evaluation was not pursued. It is noteworthy that heating a solution of the phenyldithiocarbonate (110) and AIBN in toluene at 110°C for extended periods gave no evidence of reaction in the absence of tri-*n*-butylstannane. Therefore, interaction between the redistilled tin hydride and the thiocarbonyl compound is apparently necessary for the overall thionocarbonate ester cleavage, and alcohol regeneration is not simply a deacylation artifact.

Reaction of the phenylthionocarbonate (115) with tri-*n*-butylstannane in the presence of AIBN proceeded at 80°C and gave product formation indistinguishable from that of the phenyldithiocarbonate (110) under the same conditions. However, essentially no reaction of (115) and tri-*n*-butylstannane occurred at 110°C in the absence of initiator. Reaction did occur at 140°C in the absence of AIBN to give cholesterol as the major product and cholestene as a minor product. Subjection of (115) to refluxing xylene in either the presence or absence of AIBN gave neither cholesterol nor cholestene although some decomposition of the starting material was noted upon prolonged heating. It would appear that the activation energy for initiation of reaction of (115) is higher than that of (110), but that the subsequent deoxygenation process is similar. It is possible that the difference in reactivity results from the greater stability of an α-dithio radical intermediate (118) compared to an α-thio-α-oxy radical intermediate (119).

A procedure employing phenylthionocarbonate derivatives was chosen for our deoxygenation of alcohols for several reasons. Phenyl chlorothionocarbonate (114) is a stable, effective acylating reagent that does not require strongly basic conditions to derivatize hydroxyl groups. The phenylthionocarbonate function is stable to aqueous work-up procedures and is amenable to chromatographic purification methods. Reaction of these derivatives with tri-n-butylstannane occurred under mild conditions in the presence of radical initiator and led exclusively to the desired alkane products.

SCHEME XXII



120 R = H

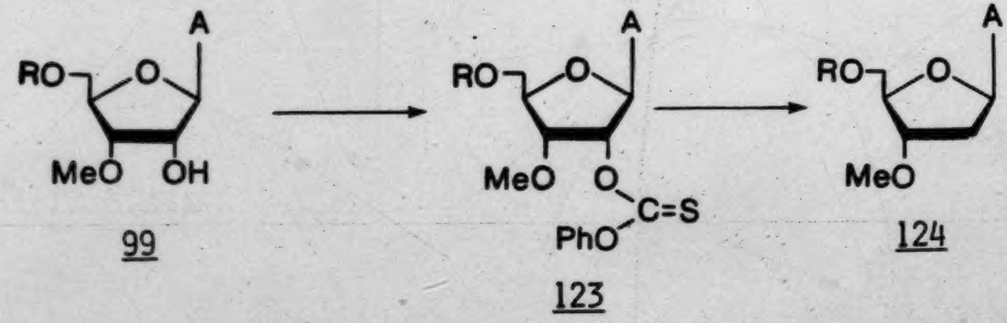
121 R = CS(OPh)

122

The deoxygenation procedure was applied to 5α,6α-epoxy-3β-cholesterol (120) following the procedure outlined for cholesterol. The intermediate phenylthionocarbonate (121) was obtained in 94% yield and reduction with tri-n-butylstannane gave 5α,6α-epoxycholestane (122) in 78% overall yield from (120).

The 5'-O-(tert-butyldiphenylsilyl)-3'-O-methyladenosine derivative (99) again was chosen as a suitable model to test the applicability of this deoxygenation method to nucleosides. Treatment of a solution of (99) in pyridine with phenyl chlorothionocarbonate (114) caused the reaction solution to slowly become coloured and gave a 60% yield of the 2'-O-phenylthionocarbonate derivative (123). The yield was not optimized, but no 6-N-acylated products were observed. Treatment of a solution of (123) in toluene with tri-n-butylstannane at 75°C in the presence of AIBN resulted in almost quantitative conversion to 5'-O-(tert-butyldiphenylsilyl)-2'-deoxy-3'-O-methyladenosine (124) by TLC. Thus, an effective means to remove the 2'-hydroxyl group from

SCHEME XXIII



nucleosides was at hand. The remaining major obstacle was the selective protection of nucleosides at O-3' and O-5' to allow specific derivatization and removal of the 2'-hydroxyl function.

A communication by Markiewicz and Wiewiorowski[109a] reported the first selective and stable 3',5' protecting group for nucleosides. We prepared this 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (95) (TPDSCl) by a modified procedure improved from that reported by Markiewicz.[109] Treatment of a solution of adenosine (6) in pyridine with TPDSCl (95) gave 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)adenosine (97) (3',5'-O-

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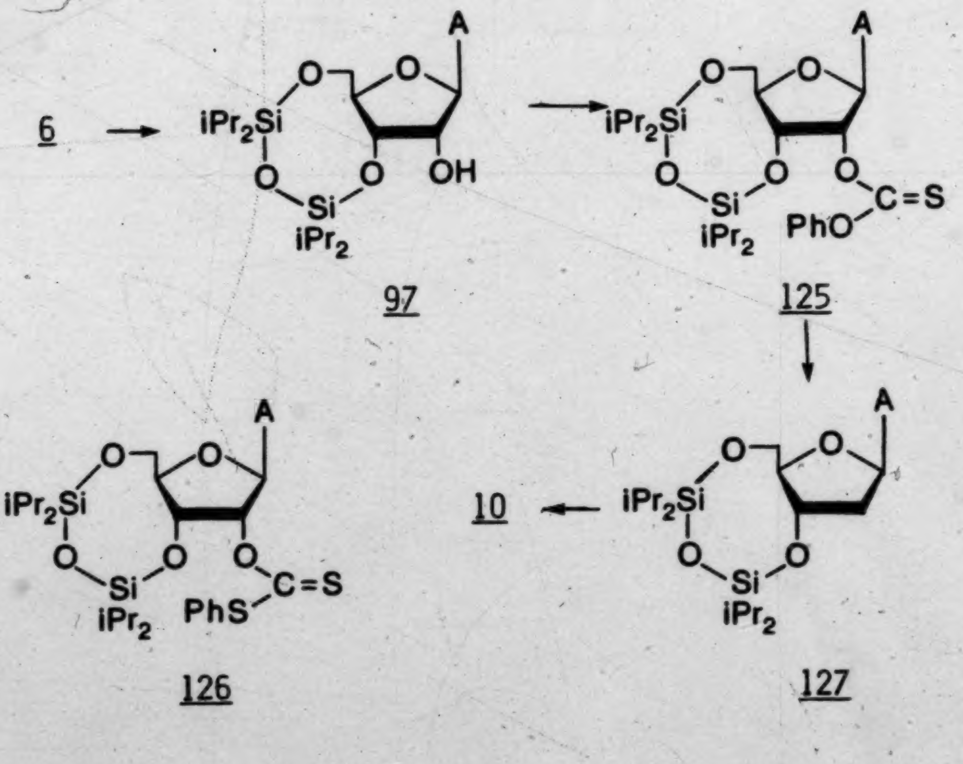


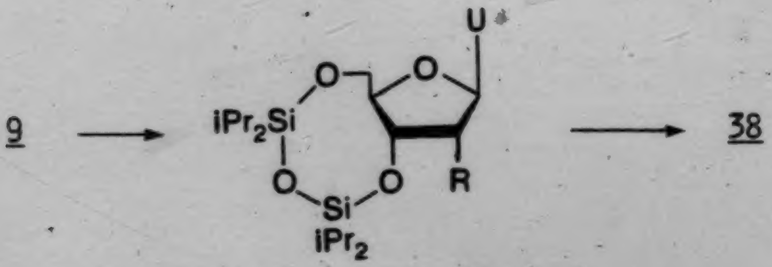
TPDSadenosine) in 80% yield. When the 3',5'-O-TPDS derivative (97) was dissolved in pyridine and treated with phenyl chlorothionocarbonate (114) at room temperature, the reaction solution slowly became coloured. However, only a trace of the 2'-O-phenoxythiocarbonyl nucleoside (125) was formed. Multiple additions of reagent (114) to the pyridine solution and prolonged reaction times gave ~20% yields of the 2'-thionocarbonate derivative (125). It appeared that pyridine catalyzed decomposition of the reagent (114). The rate of acylation of sterically accessible alcohols such as cholesterol by reagent (114) in the presence of pyridine was sufficiently rapid to compete with the decomposition process. However, this was not the case with the hindered 3',5'-O-TPDS nucleosides. A variety of solvents and catalytic bases were tested for use in the acylation reaction of 3',5'-O-TPDSadenosine (97) with phenyl chlorothionocarbonate (114). Treatment of a suspension of 3',5'-O-TPDSadenosine (97) in anhydrous acetonitrile with 2 equivalents of 4-N,N-dimethylaminopyridine (DMAP) and 1.1 equivalents of reagent (114) resulted in quantitative conversion to the 2'-O-phenoxythiocarbonyl nucleoside (125) as observed by TLC. The ^{1}H NMR spectrum of the isolated 2'-thionocarbonate (125) (Table 1) showed a marked downfield shift for the 2' H resonance in relation to that of the 2'-hydroxyl derivative (97).

This is consistent with reported ^{1}H NMR chemical shifts of C-H groups with ester and thionoester substituents.[123] It is noteworthy that we were unable to synthesize the analogous 2'-O-phenyldithiocarbonate nucleoside derivative (126) under any conditions tried using the phenyl chlorodithiocarbonate reagent (110).

Treatment of a solution of the 2'-O-phenylthionocarbonate derivative (125) in toluene with tri-n-butylstannane at 75°C in the presence of AIBN gave quantitative conversion to 2'-deoxy-3',5'-O-TPDSadenosine (127). Removal of the TPDS group from (127) was effected by subsequent treatment of the toluene reduction solution with tetra-n-butylammonium fluoride (TBAF) at 80°C. The 2'-deoxyadenosine (10) obtained was purified by anion exchange chromatography on Dowex 1 X 2 (OH^-).[50] All steps of the reaction sequence (6)→(97)→(125)→(127)→(10) proceeded efficiently without crystallization or chromatographic purification of the preceding compound. The individual reactions were performed on the crude residues obtained from evaporation of the dried organic layer after liquid-liquid partition work-up of the preceding reaction. The four step reaction sequence from adenosine (6) gave 2'-deoxyadenosine (10) in 78% overall yield. This is markedly superior to any prior synthetic method for the 2'-deoxygenation of a purine nucleoside.[30,69,71-73,75,76]

When uridine (9) was treated with TPDSCl (95) in pyridine, 3',5'-*O*-TPDSuridine (96) was obtained in excellent yield. Reaction of (96) with phenyl chlorothionocarbonate (114) in acetonitrile in the presence of DMAP proceeded quantitatively to give the 2'-*O*-phenoxythiocarbonyl-3',5'-*O*-TPDS derivative (128). It had been reported previously that the O-2→2'-cyclonucleoside of uridine (36) was formed in high yield upon heating either the cyclic 2',3'-*O*-carbonate[60-62] or thionocarbonate derivatives.[63,64] However, treatment of the 2'-thionocarbonate derivative (128) in toluene at 80°C in the presence of tri-*n*-butylstannane and AIBN resulted exclusively in 2'-deoxygenation to give the 2'-deoxy-3',5'-*O*-TPDS derivative (129). No cyclonucleoside product was observed in this reaction. Treatment of the protected 2'-deoxynucleoside (129) with

SCHEME XXV



96 R = OH

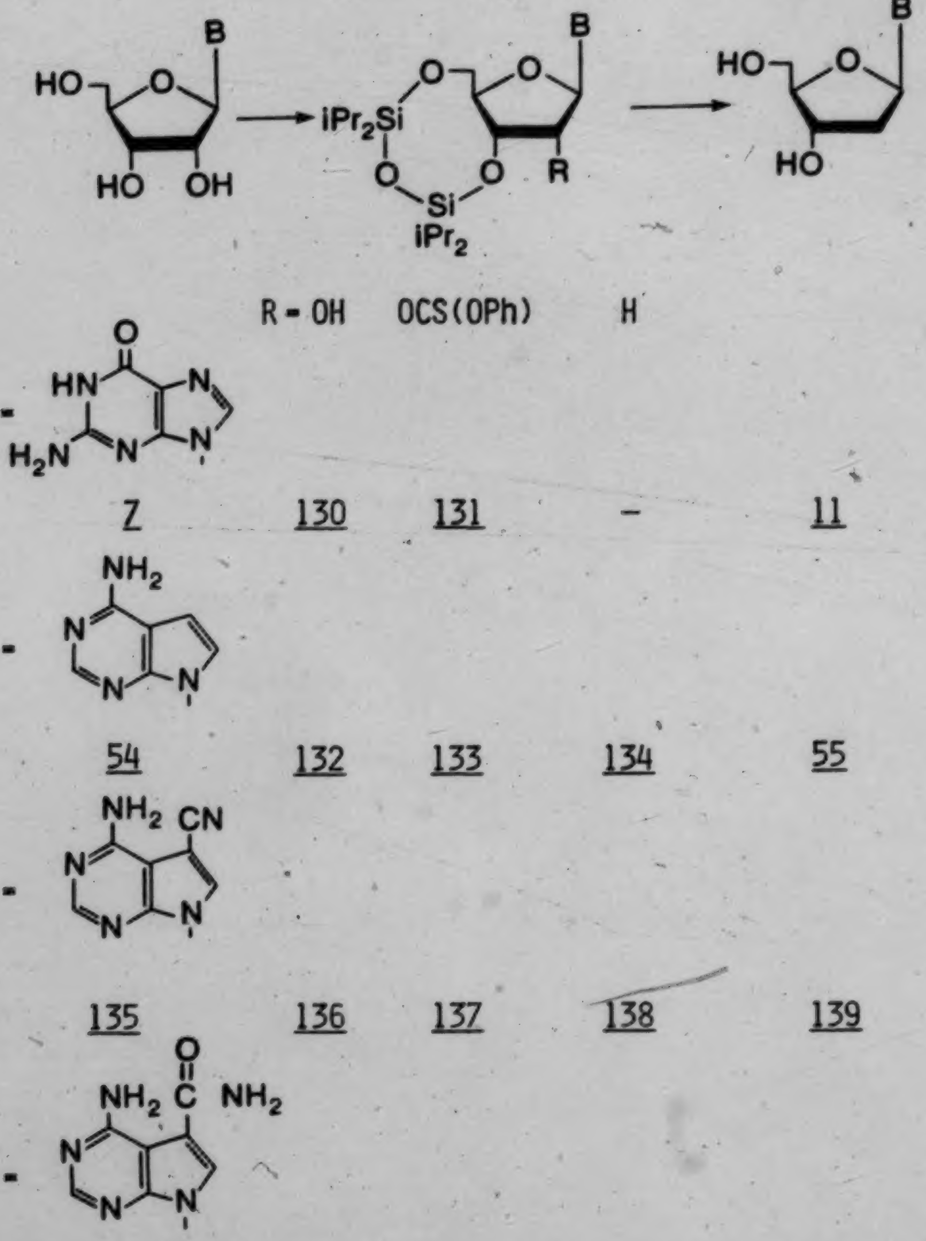
128 R = OCS(OPh)

129 R = H

TBAF was followed by chromatography on AU-4 charcoal to give 2' deoxyuridine (38) in 68% overall yield from uridine (9). This yield is slightly superior to prior procedures involving O-2→2'-cyclonucleoside interconversions.[67]

Application of our reduction method to guanosine (7) required only minor alterations. The insolubility of guanosine in pyridine restricted its conversion to 3',5'-O-TPDSguanosine (130) upon treatment with TPDSCl (95). When guanosine was dissolved in DMF/pyridine (10:1) and treated with TPDSCl (95) a good conversion to 3',5'-O-TPDSguanosine (130) occurred. Analysis of the reaction mixture by TLC indicated that formation of a minor nucleoside by-product had occurred that migrated slightly faster than the 3',5'-O-TPDS derivative (130) in all solvent systems examined. This byproduct was not investigated due to the inherent difficulty associated with purification of guanosine derivatives. To avoid possible complications the 3',5'-O-TDPS derivative (130) was isolated and crystallized in 70% yield prior to reaction with phenyl chlorothionocarbonate (114). Treatment of a suspension of (130) in acetonitrile with reagent (114) and DMAP gave 2'-O-phenoxythiocarbonyl-3',5'-O-TPDSguanosine (131) in 94% yield. Reduction of the 2'-thionocarbonate (131) with tri-n-butylstannane following the procedure

SCHEME XXVI



B		R = OH	OCS(OPh)	H	
B = guanin-9-yl	7	130	131	–	11
B = pyrrolo[2,3-d]pyrimidine (4-NH2)	54	132	133	134	55
B = pyrrolo[2,3-d]pyrimidine (4-NH2, 5-CN)	135	136	137	138	139
B = pyrrolo[2,3-d]pyrimidine (4-NH2, 5-CONH2)	140				141

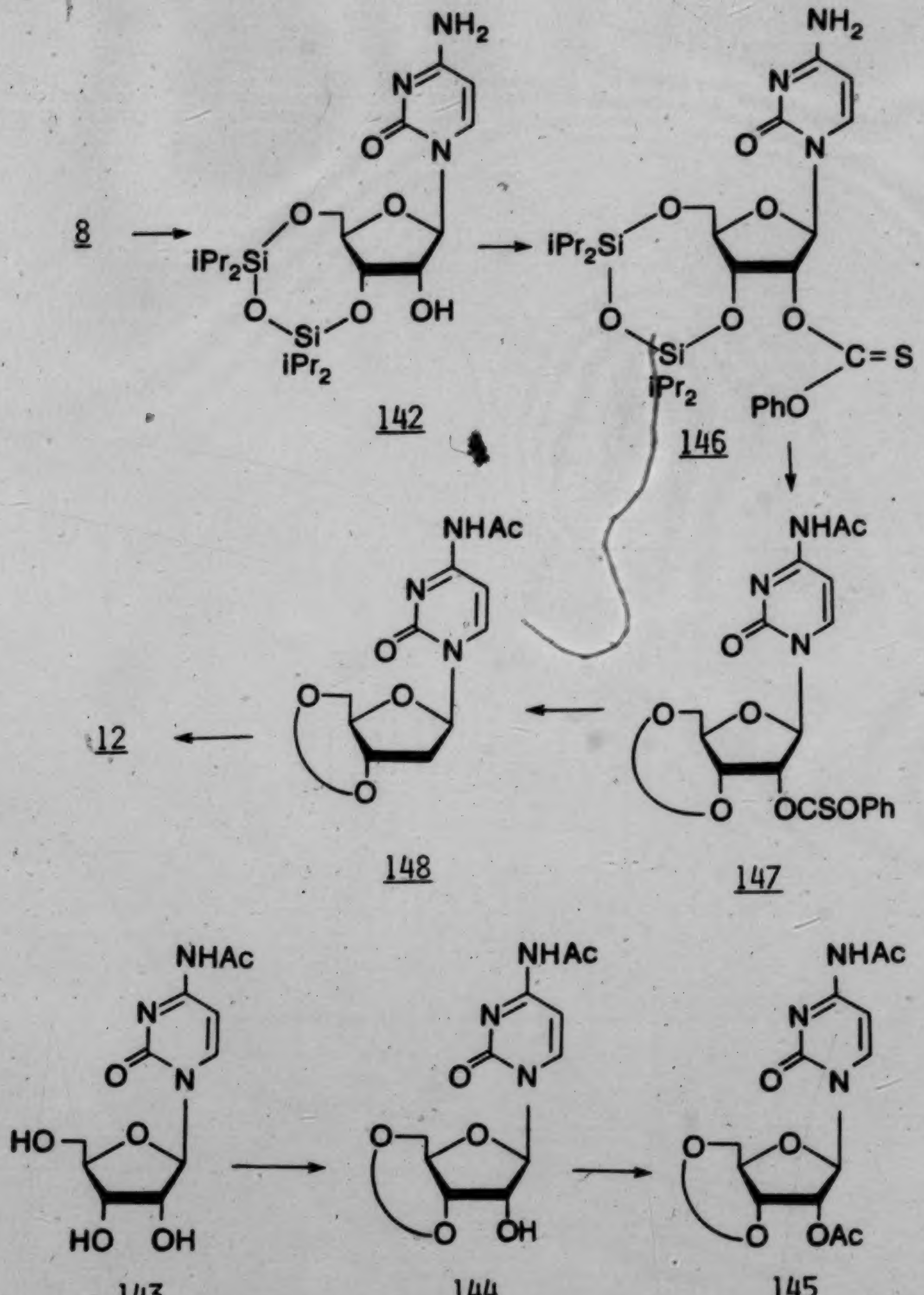
outlined previously and subsequent treatment of the reduction solution with TBAF gave 2'-deoxyguanosine (11). The crude 2'-deoxyguanosine was applied to a column of Dowex 1 X 2 (OH^-) resin and eluted using tetraethylammonium bicarbonate buffer. The overall yield of 2'-deoxyguanosine (11) from guanosine (7) was 60% and the yield of (11) from 3',5'-O-TPDSguanosine (130) was 85%.

The reaction conditions used to prepare 2'-deoxyadenosine (10) from adenosine (6) were applied to tubercidin without alteration. The overall yield of 2'-deoxytubercidin (55) from tubercidin (54) was 68%. Differences between yields obtained for 2'-deoxyadenosine (10) and 2'-deoxytubercidin (55) arise primarily from the different solubilities of the two products. The recovery of 2'-deoxytubercidin (55) from crystallization was lower than that obtained for 2'-deoxyadenosine (10).

Treatment of toyocamycin (vengicide) (135) with TPDSCl (95) in pyridine gave an 89% yield of 3',5'-O-TPDStoyocamycin (136). The excellent crystallization properties of this derivative (136) allow the high recovery. Reaction of 3',5'-O-TPDStoyocamycin with phenyl chlorothionocarbonate (114) in acetonitrile with DMAP followed by reduction of the 2'-phenylthionocarbonate derivative (137) with tri-n-butylstannane in toluene gave an 87% yield of the blocked 2'-deoxy derivative (138) from toyocamycin (135). The 2'-deoxy-3',5'-O-TPDS-toyocamycin (138) was treated with TBAF and purified by chromatography on AU-4 charcoal to give a 69% overall yield of 2'-deoxytoyocamycin (139) from toyocamycin (135). Passage of 2'-deoxytoyocamycin (139) through a column of Dowex 1 X 2 (OH^-) resin, using 40% methanol/water for elution gave 2'-deoxysangivamycin (141) in quantitative yield. This procedure for the conversion of toyocamycin (135) to sangivamycin (140) is more convenient and efficient than the method using hydrogen peroxide in aqueous base reported by Tolman et al.[124]

Treatment of cytidine (8) with TPDSCl (95) in pyridine gave 3',5'-O-TPDScytidine (142) in excellent yield. However, reaction of (142) with reagent (114) under the usual conditions gave only partial conversion to the desired 2'-O-phenoxythiocarbonyl-3',5'-O-TPDS-cytidine (146). Moderate overall conversion of (8) to this derivative (146) was obtained using six equivalents of DMAP in place of the normal two equivalents. It was assumed that the difference in behavior of cytidine (8) compared to the other nucleosides, studied was attributable to the reactive 4-amino group on the base. The selective N-4 acetylation procedure of Fox and co-workers[125] was followed to give 4-N-acetylcytidine (143). Treatment of (143) with TPDSCl (95) in pyridine

SCHEME XXVII



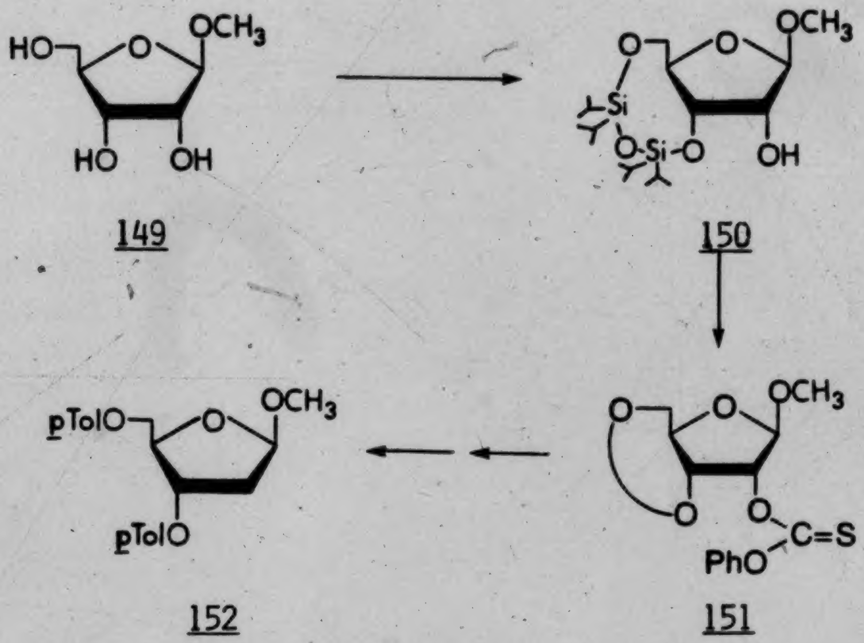
gave 4-*N*-acetyl-3',5'-*O*-TPDScytidine (*144*) in excellent yield. Surprisingly, this derivative (*144*) was totally unreactive toward phenyl chlorothionocarbonate (*114*) despite numerous attempts to promote reaction through variation of the reaction conditions. Treatment of 4-*N*-acetyl-3',5'-*O*-TPDScytidine (*144*) in acetonitrile with acetic anhydride in the presence of DMAP gave 4-*N*-acetyl-2'-*O*-acetyl-3',5'-*O*-TPDScytidine (*145*) in good yield. The cause(s) of the lack of reactivity of the 4-*N*-acetyl derivative (*144*) toward reagent (*114*) remain(s) unclear.

Subjection of 2'-*O*-phenoxythiocarbonyl-3',5'-*O*-TPDScytidine (*146*) to the standard reduction procedure resulted in a complex mixture of products. Although a minor product of the mixture was found to be the 2'-deoxy-3',5'-*O*-TPDScytidine derivative, the major contituent was unreacted 2'-thionocarbonate (*146*). Extended reaction times with multiple additions of tri-*n*-butylstannane resulted in further decomposition of reagents. The catalytic decomposition of tri-*n*-butylstannane by amines[93] was discussed in Chapter I.A. Hence the 2'-thionocarbonate derivative (*146*) was acetylated with acetic anhydride and pyridine to give 4-*N*-acetyl-2'-*O*-phenoxythiocarbonyl-3',5'-*O*-TPDScytidine (*147*). This acetylation could be accomplished directly by subsequent addition of excess acetic anhydride to the acetonitrile solution of the completed 2'-*O*-thiocarbonylation step. Treatment of (147) with tri-*n*-butylstannane and AIBN at 80°C in toluene resulted in good conversion to the 2'-deoxygenated compound (148). The 3',5'-*O*-TPDS group was removed from the 2'-deoxy derivative (148) in the usual manner and treatment of the 4-*N*-acetyl derivative with sodium methoxide in methanol followed by anion exchange chromatography on Dowex 1 X 2 (OH^-) and crystallization from ethanol gave 2'-deoxycytidine (12). An overall yield of 35% was obtained for the conversion of cytidine (8) to 2'-deoxycytidine (12).

35

Few methods exist which allow successful deoxygenation of hindered alcohols on acid sensitive carbohydrate derivatives. Treatment of methyl β-*D*-ribofuranoside (149) in pyridine with TPDSCl (95) gave an excellent yield of methyl 3',5'-*O*-TPDS-β-*D*-ribofuranoside (150). Acidic work-up conditions had to be stringently avoided since this glycoside is easily hydrolyzed. Chromatography could be performed efficiently on neutral silica if contact time with the absorbant was kept to a minimum. The 2-*O*-phenoxythiocarbonyl-3,5-*O*-TPDS derivative (151) was prepared in the usual manner. The standard reduction conditions gave clean conversion to methyl 2-deoxy-3,5-*O*-TPDS-β-*D*-*erythro*-pentofuranoside. Isolation and purification of this blocked derivative and the deprotected methyl 2-deoxy-β-*D*-*erythro*-pentofuranoside

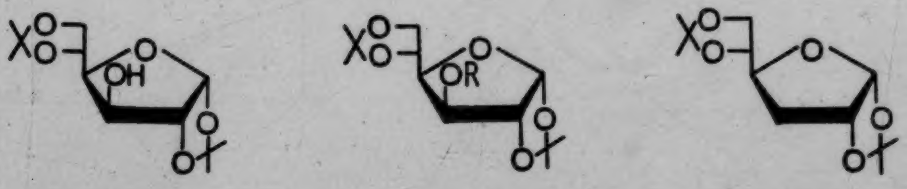
SCHEME XXVIII



were not pursued extensively owing to the acid sensitivity of these compounds. Protection of hydroxyl groups of 2'-deoxynucleosides as esters stabilizes the glycosyl bond against acid hydrolysis.[126] The crude residue of the methyl 2-deoxyfuranoside obtained from evaporation of the reduction and deprotection solution was treated with anhydrous pyridine. Treatment of this mixture with excess p-toluyl chloride gave the known methyl 2-deoxy-3,5-di-O-p-toluyl-β-D-erythro-pentofuranoside[127] (152), which was purified on neutral silica without serious decomposition. The overall yield obtained for the conversion of methyl β-*D*-ribofuranoside (149) to methyl 2-deoxy-3,5-di-*O*-*p*-toluyl-β-*D*-*erythro*-pentofuranoside (152) was 58%. This method should find synthetic applicability in the carbohydrate field for deoxygenation of hindered and acid sensitive sugars.

Finally, our deoxygenation procedure was utilized for removal of a 3-hydroxyl function of a simple protected sugar derivative. Treatment of 1,2;5,6-di-*O*-isopropylideneglucofuranose (153) in acetonitrile in the presence of DMAP with phenyl chlorothionocarbonate (114) gave the 3-*O*-phenoxythiocarbonyl derivative (154) in excellent yield. Treatment of this derivative (154) with tri-*n*-butylstannane and AIBN in toluene at 80°C gave the 3-deoxysugar (155) in 85% overall yield from the starting alcohol (153). This result is comparable to results obtained by Barton[90] for deoxygenation of the same sugar model.

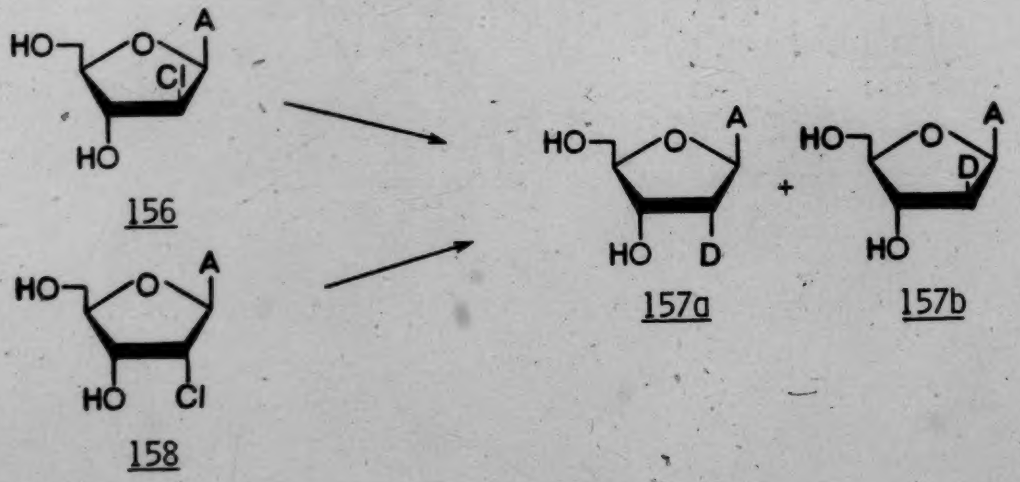
SCHEME XXIX



153 154 R = CS(OPh) 155

The deuterolysis of 9-(2-chloro-2-deoxy-β-*D*-arabinofuranosyl)adenine (156) using tri-*n*-butyltin deuteride was studied previously in our laboratory.[128] The ratio of 2'-deoxy-2'-deutero-*ribo* (157a) to 2'-deoxy-2'-deutero-*arabino* nucleoside epimers (157b) produced in this free radical mediated dehalogenation reaction was ~85:15. The observed bias in product formation was presumed to arise from the favoured attack on the bulky deuterostannane by the less hindered *ribo* face of the 2' radical (which is trans to the heterocycle at C-1). Equivalent product ratios were obtained from the epimeric 2'-chloro-*arabino* (156) and 2'-chloro-*ribo* adenosine derivatives (158). Hence, the free radical intermediate was assumed to be separated from the departing chlorine atom.

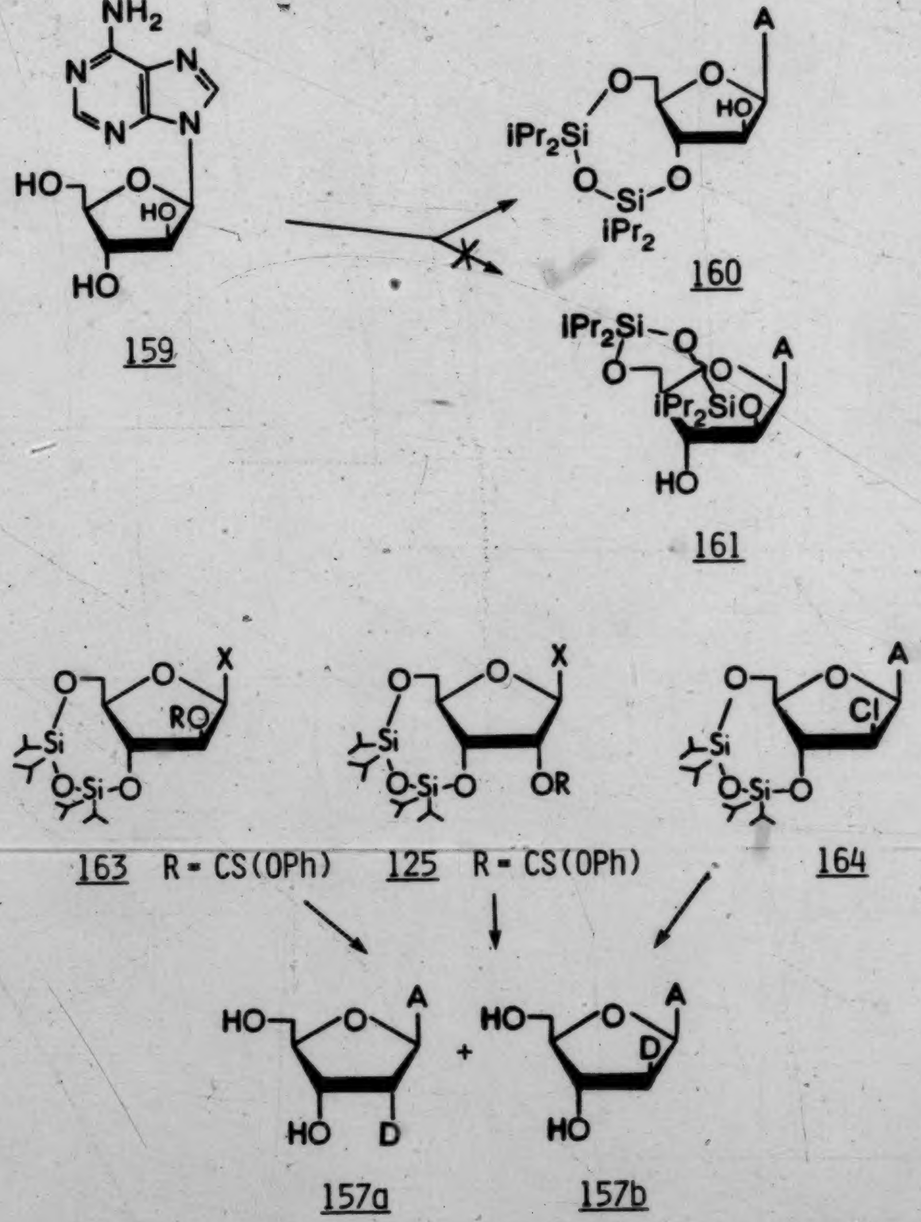
SCHEME XXX



We were interested to determine whether the present deoxygenation process with the 2'-phenylthionocarbonate derivatives would result in a similar stereochemical outcome. Treatment of a pyridine solution of 9-β-D-arabinofuranosyladenine (159) with TPDSCl (95) gave a single product (by TLC). It was not apparent by ^{1}H NMR spectroscopy whether the product was the 8-membered trans-fused 3',5'-O-TPDS derivative (160) or the 10-membered cis 2',5'-O-TPDS derivative (161). A sample of this product was acetylated for further ^{1}H NMR analysis. The marked downfield shift of the signal for the 2'-hydrogen allowed the unambiguous assignment of the 2'-O-acetyl structure (162). This confirmed that 9-(3,5-O-TPDS-β-D-arabinofuranosyl)adenine (160) was the product of the silylation reaction. The 2'-phenylthionocarbonate derivative (163) was prepared by the standard method. The ^{1}H NMR downfield shift of the peak for H-2' (see Table 5) reconfirmed our assignment of the 3',5'-O-TPDS structure (160).

Treatment of a toluene solution of the thionocarbonate (163) with tri-n-butyltin deuteride and AIBN at 80°C was followed by addition of TBAF. Anion exchange chromatography on Dowex 1 X 2 (OH^-) gave the 2'-deoxy-2'-deuteroadenosines (157a, 157b). The ratio of *ribo* to *arabino* deutero C-2' epimers was ~88:12 as evaluated by integration of the peaks for the H-2' and

SCHEME XXXI


NH2
HO
HO
HO
159
A
iPr2Si
Si
iPr2
HO
160
iPr2Si
A
iPr2Si
HO
161
X
R
163 R = CS(OPh)
X
OR
125 R = CS(OPh)
A
Cl
164
A
HO
HO
D
157a
+
A
HO
D
HO
157b

H-2" protons measured at 400 MHz.

When the identical conditions of deuterolysis and deblocking were applied to the ribo 2'-thionocarbonate derivative (125) the ratio of ribo to arabino deutero C-2' epimers obtained was identical to that obtained from the arabino 2'-thionocarbonate derivative (163). This would imply that a separated alkyl radical intermediate is formed in this reaction.

As a control study, the 2'-chloro-2'-deoxy-3',5'-O-TPDS-arabino derivative (164) was prepared in the usual manner from 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)adenine (156). Reaction of the blocked 2'-chloro derivative (164) with tri-n-butyltin deuteride at 80°C in the presence of AIBN followed by treatment with TBAF and anion exchange chromatography gave the 2'-deoxy-2'-deuteroadenosines (157a, 157b). The ratio of ribo to arabino deutero C-2' epimers again was ~88:12 as was obtained for both the epimeric ribo (125) and arabino (163) 2'-thionocarbonate derivatives. It seems likely that all three derivatives react via a common 2'-alkyl radical intermediate in this hydrogenolysis process. The results obtained are comparable to those of our previous study.[128] The greater uniformity of product ratios obtained in the present work probably arises from the greater sensitivity of the 400 MHz ^1H NMR analysis.

As discussed in our original study, the biosynthetic transformation of ribonucleotides to 2'-deoxyribonucleotides is thought to proceed by a free radical mediated enzymatic process.[128] The enzymatic conversions proceed with complete stereoselectivity and retention of configuration of attachment of the incoming H-2" to the _ribo_ face. The present 2'-deoxygenation procedure allows a biomimetic conversion with greater than 85% stereoselectivity for the "natural" _ribo_ epimer.

B. A Facile Method for Determination of Anomeric Configuration

A convenient and reliable method for determination of the anomeric configuration of an unknown natural product nucleoside or the product of a sugar base coupling synthesis has been elusive. There have been a number of empirical correlations made on various derivatives of anomeric nucleoside pairs. Small differences in spectral characteristics or other physical constants have been noted.

Originally, Hudson's rules of isorotation[129] for carbohydrate derivatives were applied to nucleosides. Ulbricht and co-workers[130] later found that the ORD/CD spectra of nucleoside anomers exhibited oppositely signed long-wavelength ("B_{2u}") transitions. This transition was found to be positive for α-purine and β-pyrimidine ribonucleosides and negative for the complementary anomers. However, both of these chiroptical methods were found to be subject to exceptions.[131]

The formation of purine[12] 3-N→C-5'-and pyrimidine[132] 2-O→C-5'-cyclonucleosides has provided unequivocal proof of the cis orientation of the base and C-5' (β-D-configuration). However, negative results from this chemical method could be misleading since certain β anomers do not form cyclonucleosides easily.[133] Furthermore, this method is not applicable to nucleosides with modified bases which lack the required functionality.

The first identification of α-adenosine was accomplished via a novel method by Wright, Tener and Khorana.[134] Synthetic α-adenosine and natural adenosine (β) were treated with periodic acid and the resulting dialdehydes were reduced with sodium borohydride. The two triols obtained had chirality remaining at C-1' only and were found to exhibit enantiomeric optical rotations. An extensive survey of oxidized-reduced nucleosides accomplished recently in these laboratories[135] revealed that triols resulting from α anomers have negative optical rotations while those from β anomers have positive rotations. However, exceptions have been observed with azapyrimidine (triazene) nucleosides.

^{1}H NMR spectroscopy has been utilized extensively for anomeric configuration determination. A number of empirical methods involving chemical shift differences have been published.[136,137] In general these deal with the anisotropic effects of the base on a specific site or function on the furanose residue. The most widely applied criterion involves chemical shift differences between the gem-dimethyl singlets of 2',3'-O-isopropylidene derivatives.[137] ^{1}H NMR spin coupling parameters have also been used to assign a trans H-1' to H-2' configuration when $J_{1',2'} \leq 1\text{-}1.5$ Hz.[138]

Other recent methods involve more advanced instrumental techniques which are not always available for routine analysis. Relaxation time correlations for carbohydrate derivatives have been studied by Hall and co-workers[139] and Guschlbauer and co-workers.[140] A direct relation between the proximity of adjacent hydrogen atoms and their relative relaxation times was shown to exist. This allows calculation of the preferred conformation and anomeric configuration.[140] ^{13}C NMR spectroscopy has also been investigated. The ^{13}C NMR chemical shifts of carbon atoms are very sensitive to steric crowding. Pairs of anomers studied[141] had C-1' resonance frequencies at lower fields when the base was cis to the 2'-hydroxyl group relative to the trans orientation.

A survey of a number of methods with a critical evaluation of their limitations has been made.[110] Since essentially all of the methods have been found to have exceptions or severe limitations and the rules formulated were based on empirical observations, unequivocal identification of a single anomer often was impossible. Furthermore, most methods require measurement of a relative difference between anomeric derivatives and both anomers must be available for comparison.

Robins and MacCoss[110] described the first generally applicable method which allows the unequivocal determination of a single anomer. This method is based on the conversion of the ribonucleoside to its 3',5'-cyclic monophosphate derivative and determination of its H-1' to H-2' NMR coupling constant. They found that the peak for H-1' appears as a singlet ($J_{1',2'} \lesssim 0.7$ Hz) for β-ribonucleoside 3',5'-cyclic monophosphates (β-3',5'-cNMP's) and a moderate to strongly coupled doublet ($J_{1',2'} \gtrsim 3.5$ Hz) for cis (α) anomers. The consistent ranges of the observed coupling constants result from the conformationally rigid cyclic nucleotides which are comprised of a trans-fused six to five membered ring system. Since the geometry of the furanose moiety is fixed, $\phi_{H-1'-H-2'}$ is virtually the same for all β-3',5'-cNMP's and anisotropic effects of the base and other variable factors (previously utilized for anomeric determination) are of negligible consequence. Thus no exceptions have been observed with this method. Furthermore, since each anomer is uniquely defined, there is no need for both anomers to be available. This method, however, has not found widespread use due to the difficulty in the synthesis of the 3',5'-cNMP's.

We observed that the ^{1}H NMR spectra of the readily available 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) (3',5'-O-TPDS) nucleoside derivatives were very similar to those of the 3',5'-cNMP's. It was concluded that the furanose ring in both types of derivatives must be restricted to a similar conformation range. A representative number of 3',5'-O-TPDS nucleosides were prepared to determine if the conformational pattern observed was consistent and as reliable as that of the 3',5'-cNMP's.

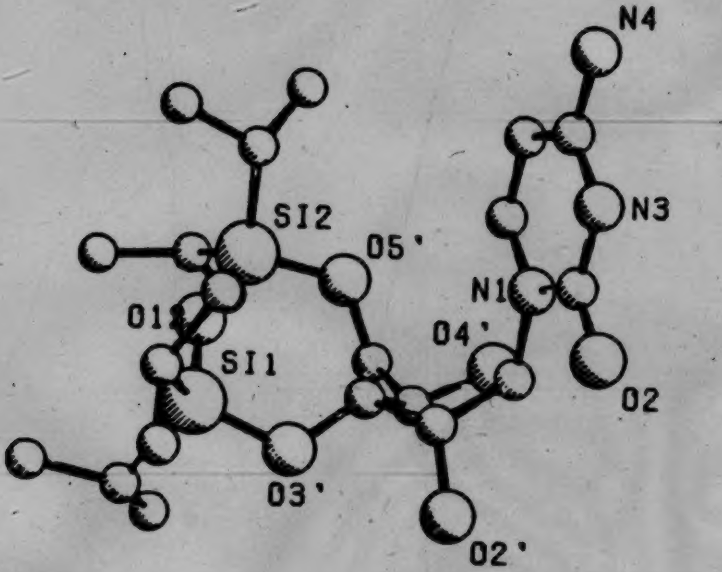
Table I contains a compilation of the ^{1}H NMR chemical shift data for the 3',5'-O-TPDS nucleosides with a trans 1'-2' configuration. The 3',5'-O-TPDS derivative of methyl β-D-ribofuranoside is included also. The coupling constants for these derivatives are listed in Table 3. The coupling constants found for the 1'-2' and 3'-4' protons indicate that the furanose ring is in the $^3T_4$-^3E-$^3T_2$ conformational range which is similar to that found in the 3',5'-cNMP's.[142] It has been estimated that $\phi_{H-1'-H-2'}$ must be in the range of 90-105° for a coupling of less than 1 Hz to occur in these furanosyl structures.[110] A small anomeric coupling was observed for the β-ribofuranosides throughout the series. However, the anomeric proton coupling of the 3',5'-O-TPDS derivatives of 9-α-D-arabinofuranosyladenine (186) and 6-N-acetyl-9-(2-O-acetyl-α-D-arabinofuranosyl-adenine (191) are not consistent with the values obtained for the β(trans 1'-2')nucleosides. This indicates that a different furanose conformation has been adopted in the cases of (186) and (191).

The 3',5'-cNMP's show much less variation in coupling parameters than the 3',5'-O-TPDS derivatives as expected from the trans-fused 6 to 5 vs. 8 to 5 membered ring systems. The anomeric proton coupling constants of the 3',5'-O-TPDS derivatives showed only a slight variation with temperature, but solvent polarity had a more pronounced effect (see Table 5). We observed that the $J_{1'-2'}$ coupling decreased for the 3',5'-O-TPDS-β-D-ribofuranosides and increased for the 3',5'-O-TPDS-α-D-ribofuranoside with increasing solvent polarity. This is consistent with a solvation-dependent conformational bias resulting from the steric demands of the bulky isopropyl groups on the TPDS fragment. It also emphasizes that the furanose ring is not geometrically locked as in the 3',5'-cNMP molecules. The altered furanose conformation observed for (186) and (191) also supports this conclusion. The $J_{1'-2'}$ values of the 2'-O-phenoxythiocarbonyl-3',5'-O-TPDS derivatives in Table 3 show some variation in relation to their 2' hydroxyl precursors. Thus steric and/or electronic demands can alter the conformation of the furanose moiety in these compounds. In contrast, derivatization of the 2' hydroxyl group of the 3',5'-cNMP's had a negligible effect on $J_{1'-2'}$.[110]

The chemical shift data for a number of cis 1'-2' examples of 3',5'-O-TPDS nucleosides are compiled in Table 2 with the respective coupling constants listed in Table 4. The anomeric coupling constants of the α ribonucleosides and β arabinonucleoside-derivatives are very similar to those found in the 3',5'-cNMP's.[110] A rationalization for the observed differences in the two types of cis 1'-2' nucleosides as well as a discussion of the strained conformations of the α-ribonucleoside cyclic monophosphates has been presented by Robins and MacCoss.[110]

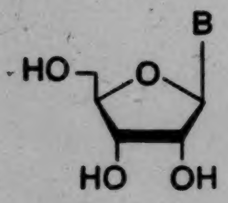
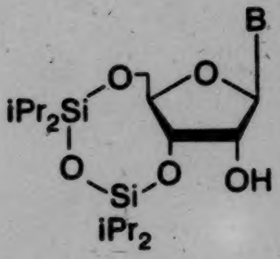
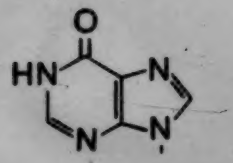
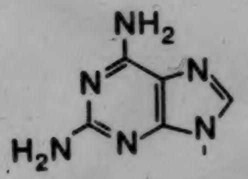
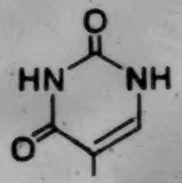
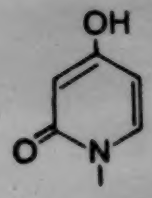
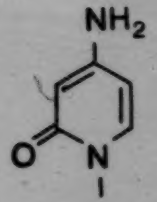
Although the 3',5'-O-TPDS derivatives have a less rigidly defined furanose conformation than the analogous 3',5'-cNMP's, a clear difference between anomers is observed. Ribofuranoside derivatives with $J_{1'-2'} \leq 1.5$ Hz can safely be assigned a β configuration since cis coupling values of this small a magnitude are geometrically precluded. It appears that cis anomers have $J_{1'-2'} \geq 3.5$ Hz. The β derivatives with an intermediate anomeric coupling value ($J_{1'-2'} \sim 2.5$ Hz) should be subjected to other methods for a definitive identification. The ease of preparation of these 3',5'-O-TPDS derivatives makes this method very convenient as well as normally definitive for evaluation of the anomeric configuration of an unknown β-ribofuranoside. Furthermore, the 3',5'-O-TPDS group can be removed easily and efficiently with fluoride anion to regenerate the parent nucleoside.

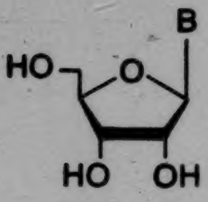
In order to verify our ^{1}H NMR conclusions concerning the furanose conformation adapted by the 3',5'-O-TPDS derivatives and to examine the trioxadisila ring fragment we subjected the cytidine compound (142) to single crystal x-ray analysis. The computer generated structure is presented below. A Dreiding molecular

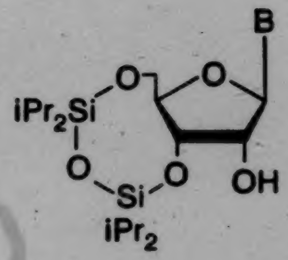


model of this compound had indicated that the C-5'-O-5' bond might assume the trans-gauche (tg) orientation as found for the 3',5'-cNMP's.[142] The 4'-5' and 4'-5" coupling constants did not contradict this assumption (see Table 3). However, a gg orientation for C-5'-O-5' also was compatible with the data and, of course, no information was available as to the conformation of the 3',5'-O-TPDS ring fragment. The x-ray analysis showed that the C-5'-O-5' bond was oriented gg for (141) in the solid state. The Si-O-Si bond angle was expanded to 158° which allows formation of an unstrained 8-membered ring. This silicon-oxygen-silicon bond expansion and accommodation of the four bulky isopropyl groups on the silicon atoms apparently result in a highly preferred conformation of the furanose in this trans-fused 8 to 5 membered ring system. The almost perfect ^3E envelope conformation observed for (141) has $\phi_{H-1'-H-2'}$ of ~90°C as anticipated from the NMR data. Table 6 illustrates the approximate relationship between estimated bond angles of adjacent hydrogen atoms in (141) and the observed ^1H NMR spin-spin coupling values.

It is interesting to note that the methyl groups of the isopropyl substituents on silicon were non-equivalent by ^{13}C NMR. The x-ray structure data revealed slightly different C-C bond lengths for the geminal methyls on each of the isopropyl methine carbons. A detailed analysis of the x-ray structure of (141) will be published in collaboration with James and Sawyer.[143]

B		
	165	166
	167	168
	169	170
	171	172
	173	174





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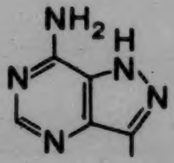

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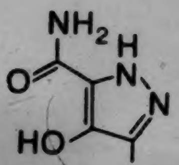

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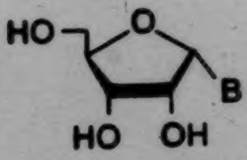
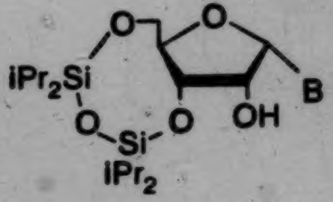
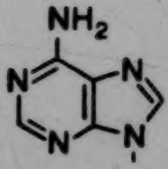
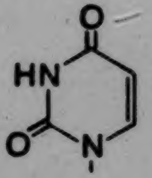
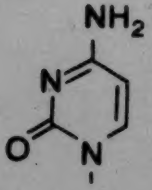
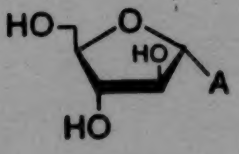
B		
	179	180
	181	182
	183	184
OMe	192	193



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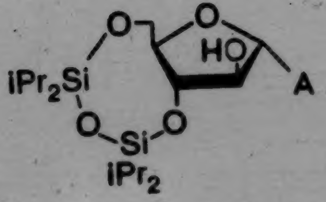

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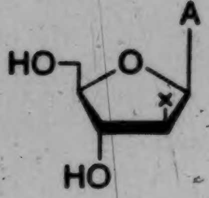
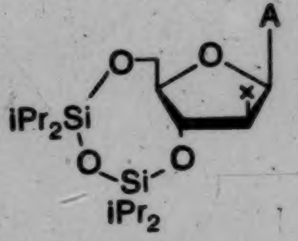
X		
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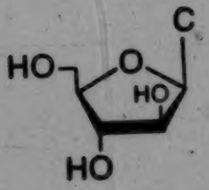
OAc	-	162
Cl	156	164
N_3	187	188



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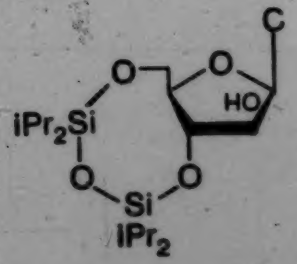

190

TABLE 1

NMR Chemical Shift Data for 3',5'-O-TPDS-β-D-ribonucleosides[i,iii)]

Compound	Base H's	C-1'	C-2'	C-3'	C-4'	C-5'	C-5"	OH	NH_2	Phenyl H's	Deuterated Solvent
97[ii)]	8.10^a 8.19^a	5.86^b	4.51^c	4.78^e	4.00^f	4.05^e	3.92^e	5.60^b	7.30^a	-	DMSO
125	8.08^a 8.32^a	6.36^b	6.53^e	5.53^e	4.00^m	4.05^e	3.98^m	-	7.43^a	o-7.19^m m-7.52^m p-7.37^m	DMSO
130	7.76^a	5.68^b	4.26^e	4.35^e	4.00^f	4.08^e	3.92^e	5.61^b	6.50^a	-	DMSO
131	7.96^a	6.11^b	6.26^e	4.89^e	4.04^m	4.07^m	3.98^m	-	6.43^a	7.17^m 7.52^m 7.36^m	DMSO
132	8.04^a 6.59^b 7.26^b	5.96^b	4.28^e	4.60^e	3.96^m	4.05^e	3.92^e	5.52^b	7.06^a	-	DMSO
133	6.40^b 7.17^b 8.28^a	6.30^b	6.32^e	5.22^e	4.08^m	4.15^e	4.06^e	-	5.35^a	7.14^m 7.42^m 7.30^m	$CDCl_3$
136	8.21^a 8.18^a	5.99^b	4.35^c	4.50^e	4.06^f	4.16^e	3.96^e	5.75^b	6.90^a	-	DMSO
137	8.17^a 8.36^a	6.32^b	6.44^e	5.30^e	4.01^m	4.01^m	4.01^m	-	7.02^a	7.17^m 7.51^m 7.35^m	DMSO
166	8.00^a 8.18^a	5.88^b	4.45^e	4.60^e	4.04^f	4.10^e	3.95^e	5.70^a	9.67^a	-	DMSO

TABLE 1 (continued)

NMR Chemical Shift Data for 3',5'-O-TPDS-β-D-ribonucleosides

COM-pound	Base H's	C-1'	C-2'	C-3'	C-4'	C-5'	C-5"	OH	NH_2	Phenyl H's	Deuterated Solvent
168	7.82^{a}	5.86^{b}	4.55^{e}	4.80^{e}	4.13^{m}	4.15^{m}	4.08^{m}	4.60^{m}	6.32^{a} 5.38^{a}	-	Acetone
96	5.53^{b} 7.69^{b}	5.54^{a}	4.14^{m}	4.16^{e}	3.97^{f}	4.12^{e}	3.92^{e}	5.58^{b}	-	-	DMSO
128	5.85^{b} 7.80^{b}	6.00^{a}	6.08^{b}	4.60^{e}	4.16^{m}	4.20^{m}	4.10^{m}	-	-	7.19^{m} 7.52^{m} 7.37^{m}	$CDCl_3$
142	5.68^{b} 7.72^{b}	5.57^{a}	3.92^{c}	4.09^{e}	4.01^{f}	4.17^{e}	3.92^{e}	5.61^{b}	7.16^{b}	-	DMSO
144	7.23^{b} 8.16^{b}	5.62^{a}	4.08^{m}	4.08^{m}	4.08^{m}	4.24^{e}	3.94^{e}	5.83^{b}	-	-	DMSO
146	5.87^{b} 7.71^{b}	5.79^{b}	6.08^{e}	4.84^{e}	4.03^{m}	4.14^{m}	3.94^{m}	-	7.34^{a}	7.19^{m} 7.52^{m} 7.37^{m}	DMSO
147	7.16^{m} 7.44^{m}	6.09^{a}	6.10^{b}	4.52^{e}	4.20^{m}	4.32^{m}	4.06^{e}	-	-	7.22^{m} 7.32^{m} 7.44^{m}	$CDCl_3$
172	5.55^{b} 5.82^{e} 7.65^{b}	5.75^{a}	4.10^{m}	4.16^{m}	4.05^{m}	4.00^{m}	4.00^{m}	5.75^{m} 5.85^{m}	-	-	DMSO

TABLE 1 (continued)

NMR Chemical Shift Data for 3',5'-O-TPDS-β-D-ribonucleosides

Compound	Base H's	C-1'	C-2'	C-3'	C-4'	C-5'	C-5"	OH	NH_2	Phenyl H's	Deuterated Solvent
174	5.50^a 5.60^b 7.52^b	5.85^a	4.16^m	4.25^e	4.16^m	4.18^m	3.95^e	4.20^m	7.20^a	-	$CDCl_3$
170	8.32^a	4.52^a	3.96^b	4.13^e	3.84^m	4.04^m	3.87^m	5.20^b	-	-	DMSO
178	-	5.04^b	4.52^e	4.33^e	4.00^m	4.16^m	4.10^m	5.12 5.20	4.90^a 6.85^a	-	Acetone
176	8.25^a	5.25^b	4.68^e	5.28^m	4.05^m	4.05^m	4.05^m	4.05^m	6.90^a	-	Acetone
150	-	4.79^b	3.97^e	4.08^c	3.84^m	3.89^m	3.76^m	4.10^m	-	-	DMSO

i) Chemical shifts in δ ppm downfield from Me_4Si(internal)

ii) a = singlet b = doublet c = triplet d = quartet e = doublet of doublets
f = doublet of triplets g = doublet of doublet of doublets m = multiplet

iii) In all cases above, the resonances of the iPr H's on the disiloxyl group appeared as a complex multiplet at δ 1.05-1.10.

TABLE 2

NMR Chemical Shift Data for α-D-ribo, β-D-arabino, and α-D-arabino 3',5'-O-TPDS-nucleosides.[i)]

Compound	Base H's	C-1'	C-2'	C-3'	C-4'	C-5'	C-5"	OH	NH_2	Deut. Solvent
180	8.16^a 8.26^a	6.38^b	4.34^m	4.50^e	4.20^m	4.02^e	3.91^e	5.79	7.30^a	DMSO
182	5.57^b 7.54^b	6.02^b	4.18^m	4.36^e	4.13^f	4.03^e	3.87^e	5.40^b	7.07^b	DMSO
184	5.67^b 7.47^b	6.01^b	4.13^e	4.33^e	4.07^f	4.00^e	3.86^e	5.62^b	-	DMSO
193	-	4.79^b	3.97^e	4.08^c	3.84^m	3.89^m	3.76^m	4.07^m	-	DMSO
160	8.04^a 8.11^a	6.21^b	4.55^m	4.55^m	3.80^m	4.12^e	3.92^e	5.80^b	7.30^a	DMSO
162	8.40^a 8.58^a	6.56^b	5.64^m	5.08^m	4.05^m	4.05^m	4.05^m	-	-	DMSO
164	8.14^a 8.35^a	6.50^b	4.66^e	4.79^c	3.94^m	4.23^e	4.10^e	-	5.95^a	$CDCl_3$
188	8.10^a 8.11^a	6.40^b	4.90^m	4.90^m	3.94^m	4.24^e	3.94^m	-	7.36^a	DMSO
190	5.66^b 7.44^b	6.07^b	4.22^d	4.07^e	3.68^m	3.98^e	3.92^e	5.63^b	7.11^b	DMSO
186	7.98^a 8.26^a	5.81^b	4.78^e	4.54^e	4.16^f	4.10^e	4.04^e	-	5.91^a	$CDCl_3$
191	8.64^a 8.69^a	6.20^b	6.26^m	4.61^m	4.61^m	3.98^m	3.98^m	-	-	DMSO

i) See Table 1 footnotes for explanation of symbols and units.

TABLE 3

NMR Spin-Spin Coupling Values for 3',5'-O-TPDS-β-D-ribonucleosides i)

Compound	J_{5-6}	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5'}$	$J_{4'-5''}$	$J_{5'-5''}$	$J_{2'-2'OH}$
97	-	0.9	5.0	8.0	3.2	2.6	12.6	4.7
125	-	1.2	5.5	8.7	4.1	m	13.0	-
130	-	1.6	5.0	8.0	3.2	2.6	13.0	5.2
131	-	2.6	5.8	7.0	m	m	m	-
132	3.6	s ii)	5.5	7.7	2.0	2.3	12.5	4.7
133	3.7	1.5	5.2	8.6	3.2	2.7	13.0	-
136	-	s	5.0	8.5	2.6	2.4	13.0	5.0
137	-	1.3	5.5	8.5	m	m	m	-
166	-	1.5	5.2	8.4	2.8	3.2	12.8	-
168	-	1.5	5.0	7.5	3.5	2.0	11.5	-
96	8.0	s	4.7	8.4	2.6	2.6	13.2	4.5
128	8.0	s	5.3	10.0	m	m	m	-
142	7.6	s	4.4	5.8	2.2	2.7	13.0	4.4

TABLE 3 (continued)

NMR Spin-Spin Coupling Values for 3',5'-O-TPDS-β-D-ribonucleosides

Compound	J_{5-6}	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5'}$	$J_{4'-5''}$	$J_{5'-5''}$	$J_{2'-2'OH}$
146	-	s	5.5	8.5	m	m	m	-
147	-	s	4.2	9.5	m	m	13.8	-
172	7.5 (J_{3-5}=2.5)	s	m	m	m	m	m	-
174	7.0	s	5.0	8.5	1.8	2.5	14.0	m
170	-	s	4.5	8.5	m	m	12.5	4.0
~~178~~	-	2.7	5.6	8.0	4.8	3.0	12.5	-
176	-	2.0	5.2	m	m	m	m	m
150	-	s	4.5	7.5	3.0	5.9	11.5	4.2

i) Coupling in Hz

ii) $J_{1'-2'} \lesssim 0.5$ Hz. This is the lower limit of resolution for instrumentation used.

TABLE 4

NMR Spin-Spin Coupling Values for α-D-ribo, β-D-arabino, and α-D-arabino 3',5'-O-TPDS-nucleosides[1)]

Compound	J_{5-6}	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5'}$	$J_{4'-5''}$	$J_{5'-5''}$	$J_{2'-2'OH}$
180	-	4.0	5.0	8.0	4.0	3.0	12.5	m
182	7.6	3.5	4.0	9.1	3.0	2.5	12.8	4.6
184	8.0	3.6	4.0	9.0	2.8	2.4	13.0	4.4
193	-	4.0	6.5	5.0	3.0	4.0	10.5	m
160	-	6.3	8.0	8.0	4.0	2.5	12.5	5.8
162	-	6.7	m	m	m	m	m	m
164	-	6.0	8.0	8.0	4.0	3.0	13.0	-
188	-	6.6	m	m	5.5	m	13.0	m
190	7.4	6.2	7.0	7.8	3.8	3.0	13.0	5.8
186	-	5.7	8.1	8.7	3.0	3.0	11.0	-
191	-	5.8	m	m	m	m	m	-

1) Coupling in Hz

TABLE 5

Solvent Dependency of H-1'-H-2' Spin-Spin Coupling Values for Selected 3',5'-O-TPDS nucleosides.[i)]

Compound	$J_{1'-2'}$	Deuterated Solvent
97	0.9	DMSO
	1.4	$CDCl_3$
132	$s^{ii)}$	DMSO
	1.5	$CDCl_3$
176	2.3	DMSO
	2.0	CD_3COCD_3
	3.2	$CDCl_3$
184	3.5	DMSO
	2.9	$CDCl_3$
186	6.2	DMSO
	5.7	$CDCl_3$

i) Coupling in Hz

ii) $J_{1'-2'} \leq 0.5$ Hz (see Table 3).

TABLE 6

Calculated and Observed Spin-Spin Coupling Values of 3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)cytidine

H atoms	Calcd. Torsion Angle[i)]	J_{Calcd}[ii)]	$J_{Observed}$
H-1'-H-2'	89.8	0	0
H-2'-H-3'	41.6	4.97	4.4
H-3'-H-4'	157.7	10.09	8.8
H-4'-H-5"	44.4	4.50	2.7
H-4'-H-5'	74.8	0.41	2.2
OH-2'-H-2'	36.4	5.84	4.4

i) Torsional angles calculated based on a 1.08Å carbon-hydrogen bond length and optimized sp^3 geometry for the carbon atoms involved. Angles were obtained through a least-squares calculation from X-ray data and are given in degrees.

ii) J_{H-H} Coupling values obtained from $J_{H-H}=10.5\cos^2\theta-1.2\cos\theta$.[150] Coupling in Hz.

EXPERIMENTAL

A. General Procedures

Melting points were determined on a Reichert microstage apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Bruker WH-200 or Bruker WH-400 spectrometers operating in the FT mode, with Me_4Si as internal reference normally in Me_2SO-$\underline{d}_6$ unless specified otherwise. Ultraviolet (uv) spectra were recorded on a Cary 15 spectrophotometer and infrared (ir) spectra on a Nicolet 7199 FT(IR) instrument. Optical rotations were determined using a Perkin-Elmer Model 141 polarimeter with a 10 cm 1 ml microcell. Mass spectra (M.S.) were determined by the mass spectrometry laboratory of this department on an AEI MS-50 instrument with computer processing at 70 eV using a direct probe for sample introduction. Elemental analyses were determined by the Microanalytical Laboratory of this department or by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Evaporations were effected using Buchler rotating evaporators equipped with Dewar "dry-ice" condensers under water aspirator or mechanical oil pump vacuum at 40°C or cooler. Thin layer chromatography (TLC) was performed on E. Merck chromatographic sheets (silica gel 60 F_{254}, layer thickness 0.2 mm, catalogue 5775) with sample observation under UV light (2537 Å). Preparative

TLC was performed on glass plates coated with Merck silica gel PF 254. The solvents used for TLC were different ratios of methanol-chloroform (1:50, 1:20, 1:10) and the upper phase of EtOAc-nPrOH-H_2O (4:1:2). Silica gel column chromatography was performed using Mallinckrodt CC-7 (200 mesh) silica gel. Anion exchange chromatography was carried out on Dowex 1 X 2 resin in the hydroxide form.

The carbon used for chromatography was Barnebey-Cheney AU-4 charcoal. It was conditioned by the following treatments. It first was washed with methanol and then chloroform. After drying it was refluxed with 1 N aqueous HCl (with the acid solutions being replaced periodically) until the supernatant solution remained colourless, with water to neutrality, and then was refluxed with 10% aqueous NaOH (again with periodic replacement of the solution) until the supernatant remained colourless. The charcoal then was washed with water to neutrality, with methanol, and with chloroform. Finally it was air dried at room temperature.

All solvents used were of reagent grade and were distilled prior to use. Purification of most solvents and reagents was accomplished according to methods described in reference 144. Dimethylformamide (DMF) was purified according to the azeotropic distillation procedure described in reference 145. All dried solvents were stored over Davison 4 Å molecular sieves purchased from the Fisher Scientific Company.

The reaction sequence developed for the 2'-deoxygenation of nucleosides is a general four step procedure which is described in detail for adenosine. Subsequent experimental descriptions will refer to Procedure A: the silylation step; Procedure B: the thioacylation step; Procedure C: the reduction step using n-Bu_3SnH; Procedure D: the desilylation step. The standard work-up procedure refers to the partitioning of a reaction residue between ethyl acetate and water followed by washing the organic phase with cold 1 N HCl, H_2O, saturated $NaHCO_3/H_2O$ solution, saturated $NaCl/H_2O$ solution, drying (Na_2SO_4), filtering, and evaporating the solvent. This procedure is detailed in the first reaction with adenosine.

Abbreviations used are: TPDSCl = 1,1,3,3-Tetraisopropyl-1,3-dichlorodisiloxane; PTC chloride = phenyl chlorothionocarbonate; DMAP = 4-N,N-Dimethylaminopyridine; and AIBN = Azobisisobutyronitrile. Skelly B represents the petroleum ether fraction which boils between 60-90°C. Upon distillation the fraction boiling at 63-65°C was recovered.

B. Syntheses

1,1,3,3-Tetraisopropyl-1,3-disiloxane (95a)

The procedure of Gilman and Clark[146] was followed resulting in a 35-40% direct yield of (95a) based on starting trichlorosilane. The by-product diisopropylsilanol obtained was converted to the disiloxane by addition of P_2O_5 and distillation of the supernatant. This gave a combined yield of 90% of (95a): bp 104°C/10 mm Hg; n_D^{20} = 1.4335; ir/neat/cm^{-1} γ SiOH = 2110; M.S. m/z 246 (100%, M^+), 203 (64%, M^+-iPr); (lit.[109] bp 95°C/15 mm Hg).

1,1,3,3-Tetraisopropyl-1,3-dichlorodisiloxane (TPDSCl) (95)

To 50 g (0.20 mol) of (95a) was added 500 ml of CCl_4, and 20% of the solvent was removed by distillation at atmospheric pressure. The dried solution was cooled to -20°C and stirred vigorously while dry Cl_2 was introduced for 1 h. The reaction vessel was then subjected to aspirator vacuum at 20 mm Hg for 5 min to remove dissolved HCl formed in the reaction. Introduction of Cl_2 then was continued for 1 h. The above procedure was repeated until the solution became yellow permanently. The CCl_4 was evaporated *in vacuo* and the residue was distilled at 68-70°C/0.05 mm Hg to give 48 g (75%) of (95): n_D^{20} = 1.4550; M.S. m/z 271 (M^+-iPr); (lit.[109] 120°C/15 mm Hg).

3β-Cholesteryl phenylthionocarbonate (115)

To a stirred solution of 3.87 g (10 mmol) of cholesterol (109) in 60 ml of dichloromethane was added 3 ml (37 mmol) of anhydrous pyridine and 2.0 ml (11 mmol) of phenyl chlorothionocarbonate (PTC chloride) (114).[122] After 2 h the solvents were evaporated in vacuo and the residue was subjected to the standard work-up procedure. Crystallization from acetone gave 5.0 g (96%) of (115): mp 162-163.5°C; M.S. m/z 369.3493 (85%, M^+-OCSOϕ = 369.3521), 368.3436 (100%, M^+-HOCSOϕ); Anal. Calcd. for $C_{34}H_{50}O_2S$: C 78.11, H 9.64, S 6.12. Found: C 78.10, H 9.37, S 6.11.

Cholest-5-ene (112)

To 1.046 g (2 mmol) of (115) was added 30 ml of toluene, 800 μl (3 mmol) of n-Bu_3SnH and 65 μl (0.4 mmol) of di-tert-butylperoxide. The solution was refluxed under nitrogen for 3 h before 3 ml of a 1 M solution of n-Bu_4NF in tetrahydrofuran was added. After refluxing for 4 h the solvents were evaporated in vacuo and the residue was chromatographed on a column of alumina (20 g, 3 x 15 cm) using Skelly B as the eluant. Evaporation of the eluants and crystallization of the residue from ethanol gave 620 mg (84%) of (112): mp 92-94°C; M.S. m/z 370 (100%, M^+) 371 (30%, M^++1); Anal. Calcd. for

$C_{27}H_{46}$: C 87.49, H 12.51. Found: C 87.32, H 12.35; (lit.[90] mp 90-92°C).

5α,6α-epoxy-3β-cholesteryl phenylthionocarbonate (121)

To 2.01 g (5 mmol) of 5α,6α-epoxy-3β-cholesterol[147] (120) dissolved in 30 ml of dichloromethane was added 15 ml (19 mmol) of pyridine and 1.0 ml (5.5 mmol) of PTC chloride (114). The solution was stirred for 2 h before the solvent was removed *in vacuo*. After the standard work-up procedure the residue was crystallized from acetone to give 2.48 g (92%) of (121): mp 191-194°C; M.S. m/z 385.3453 (77%, M^+-OCSOϕ), 384.3398 (100%, M^+-HOCSOϕ); *Anal*. Calcd. for $C_{34}H_{50}O_3S$: C 75.79, H 9.35, S 5.95, O 8.91. Found: C 75.73, H 9.04, S 6.00, O 9.13.

5α,6α-Epoxycholestane (122)

To 1.078 g (2 mmol) of (121) dissolved in 30 ml of toluene was added 800 μl (3 mmol) of *n*-Bu_3SnH and 65 μl (0.4 mmol) of di-*tert*-butylperoxide. The solution was refluxed under nitrogen for 3 h. The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of alumina (20 gm, 3 x 15 cm) using Skelly B as the eluant. Evaporation of the appropriate fractions and crystallization of the residue from acetone gave 603 mg (78%) of (122): mp 74-75°C; M.S. m/z 386.3552 (100%, M^+ = 386.3549); *Anal*. Calcd. for $C_{27}H_{46}O$:

C 83.86, H 12.00, O 4.14. Found: C 83.81, H 11.86, O 4.05; (lit.[148] mp 74-75°C).

3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-adenosine (97)

To 267 mg (1 mmol) of dried adenosine (6) suspended in 10 ml of anhydrous pyridine was added 320 μl (1 mmol) of (TPDSCl) (95) and the mixture was stirred at room temperature for 3 h. Pyridine was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic phase was washed with 2 X 20 ml of cold 1 N HCl, H_2O, saturated $NaHCO_3/H_2O$ solution, saturated $NaCl/H_2O$ solution, dried (Na_2SO_4), filtered, and evaporated. The resulting amorphous product was of sufficient purity for direct use in subsequent reactions. For characterization, this material was chromatographed on a column of silica (10 g, 2 x 10 cm) using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from CH_3CN gave 433 mg (85%) of (97): mp 98-99.5°C; uv (0.1 N HCl) max 257 nm (ε 14,900); (0.1 N NaOH) max 259 nm (ε 15,100); M.S. m/z 509.2485 (8.8%, $M^+[C_{22}H_{39}N_5O_5Si_2]$ = 509.2490), 466.1924 (100%, M^+-iPr), 164.0573 (17%, BHCHO), 136.0621 (19%, B+2H); *Anal*. Calcd. for $C_{22}H_{39}N_5O_5Si_2$: C 51.83, H 7.71, N 13.74. Found: C 51.65, H 7.92, N 13.73.

2'-*O*-Phenoxythiocarbonyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)adenosine (**125**)

To the vacuum-dried residue of crude (**97**) was added 15 ml of anhydrous acetonitrile and 250 mg (2 mmol) of 4-*N*,*N*-dimethylaminopyridine (DMAP). A 200 µl (1.1 mmol) aliquot of PTC chloride (**114**) was added and the solution was stirred at room temperature for 16 h. Solvent was removed *in vacuo* and the residue was subjected to the standard work-up procedure. The resulting product was sufficiently pure to be used directly in the reduction step. Purification of this material was achieved by chromatography on a column of silica (10 g, 2 x 10 cm) using chloroform and 1.5% methanol/chloroform as eluants. Evaporation of the appropriate fractions gave 586 mg (90%) of (**125**) as an oil with uv (EtOH) max 259 nm, 228 nm, min 245 nm; M.S. m/z 602.1924 (6.1%, M$^+$-iPr[$C_{26}H_{36}N_5O_6Si_2S$] = 602.1927), 492.2471 (12%, M$^+$-OCSOϕ), 491.2473 (7.1%, M$^+$-HOCSOϕ), 449.1984 (8.6%, M$^+$-iPr-OCSOϕ), 164.0576 (5.4%, BHCHO) 135.0545 (2.0%, B+H).

2'-Deoxy-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-adenosine (**127**)

The crude (**125**) was dissolved in 20 ml of distilled toluene and 32 mg (0.2 mmol) of azobisisobutyronitrile

(AIBN) and 400 µl (1.5 mmol) of n-Bu_3SnH were added. The solution was deoxygenated with oxygen-free nitrogen for 20 min and then heated to 75°C for 3 h. Solvent was evaporated *in vacuo* and the residue was chromatographed on a column of silica (10 g, 2 x 10 cm) using chloroform as the eluant. Evaporation of the eluant and crystallization of the residue from ethanol gave 370 mg (75%) of (127): mp 113-114.5°C; uv (MeOH) max 259 nm (ε 14,000); (0.1 N HCl) max 257 nm (ε 13,500); M.S. m/z 493.2538 (18%, M^+ = 493.2544), 450.1986 (100%, M^+-iPr), 164.0574 (11%, BHCHO), 162.0778 (1.3%, $BHCH{=}CH_2$); Anal. Calcd. for $C_{29}H_{39}N_5O_4Si_2$: C 53.51, H 7.96, N 14.18. Found: C 53.31, H 7.90, N 13.93.

2'-Deoxyadenosine (10)

Deprotection of crude (127) was effected by addition of 2 molar equivalents of n-Bu_4NF (as a 1 M solution in THF) directly to the above reduction mixture. The solution was heated for an additional hour at 75°C. Solvent was evaporated and the residue was partitioned between ether and water. The aqueous phase was applied to a column of Dowex 1 X 2 (OH^-) resin. Elution of the product with water, evaporation and crystallization of the residue from ethanol/ether gave 195 mg (86%) of (10): mp 191-192°C; M.S. m/z 251.1073 (7.1%, M^+ [$C_{10}H_{13}N_5O_3$] = 251.1082), 162.0827 (100%, $BHCH{=}CH_2$), 135.0660 (99%, B+H); (lit. [149] mp 187-189°C). This product was identical to naturally occurring 2'-deoxyadenosine by the usual criteria.

Treatment of 1.068 g (4 mmol) of adenosine (6) by the four step sequence (6 → 97 → 125 → 127 → 10) without purification of intermediates gave 780 mg (3.1 mmol) of recrystallized 2'-deoxyadenosine (10) in 78% overall yield.

3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)uridine (96)

The conditions of Procedure A were followed using 972 mg (4 mmol) of dried uridine (9), 50 ml of anhydrous pyridine and 1.3 ml (4 mmol) of TPDSCl (95). After the standard work-up procedure a small portion of the crude residue was chromatographed on silica using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions yielded an oil with uv (MeOH) max 262 nm (ε 9,600); (0.1 N HCl) max 262 (ε 9,600); (0.1 N NaOH) max 262 nm (ε 7,000); M.S. m/z 486.2262 (12%, $M^+[C_{21}H_{38}N_2O_7Si_2]$ = 486.2268), 443.1718 (100%, M^+-iPr).

2'-O-Phenoxythiocarbonyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)uridine (128)

The conditions of Procedure B were applied to the residue of crude (96) using 60 ml of anhydrous acetonitrile, 1 g (8 mmol) of DMAP, and 800 µl (4.4 mmol) of PTC chloride (114). After the standard work-up procedure a small sample of the crude residue was chromatographed on silica using chloroform and 2% methanol/chloroform as eluants. Evaporation of the eluate gave an oil with uv (MeOH) max 262, 232 nm, min 245 nm; M.S. m/z 469.2206 (0.5%, M^+-OCSOϕ[$C_{21}H_{37}N_2O_6Si_2$] = 469.2172), 426.1577 (32%, M^+-OCSOϕ-iPr), 425.1554 (100%, M^+-OCSOϕ-iPr-H).

2'-Deoxyuridine (38)

The crude (128) was subjected to the reduction conditions of Procedure C using 75 ml of toluene, 1.6 ml (6.0 mmol) of n-Bu_3SnH, and 130 mg (0.8 mmol) of AIBN. After the reaction was complete, the deblocking step of Procedure D was performed directly. Solvents were evaporated and the residue was partitioned between ether and water. The aqueous phase was stirred with 10 g of carbon. To a glass column (2 x 30 cm) was added 3 g of carbon and the slurry of carbon containing the absorbed nucleoside was layered on top. The column was washed thoroughly with water before a stepwise gradient from 20% ethanol/H_2O to 40% ethanol/H_2O was applied. Evaporation of the appropriate fractions and crystallization of the residue from ethanol/ether gave 620 mg (68% overall from (9)) of (38): mp 162-163°C; M.S. m/z 228.0742 (4.1%, M^+[$C_9H_{12}N_2O_5$] = 228.0746), 139.0726 (2.5%, BHCH=CH_2), 112.0278 (25%, B+H); (lit.[149] mp 163°C).

3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-guanosine (130)

To 1.132 g (4 mmol) of dried guanosine (7) suspended in 60 ml of anhydrous DMF was added 4 ml of anhydrous pyridine and 1.3 ml (4 mmol) of TPDSCl (95). The mixture was stirred for 5 h and then added slowly to 1 ℓ of vigorously stirred ice water. The resulting precipitate was collected by filtration and washed thoroughly with water. Crystallization from 95% ethanol gave 1.47 g (70%) of (130): mp >250°C (decomp.); uv (MeOH) max 256 nm (ε 14,300), (0.1 N HCl) max 256 nm (ε 11,700), (0.1 N NaOH) max 263 nm (ε 11,400); M.S. m/z 525.2443 (24%, $M^+[C_{22}H_{39}N_5O_6Si_2]$ = 525.2435), 526.2464 (9%, M^++1), 483.1912 (41%, M^++1-iPr), 482.1876 (91%, M^+-iPr); Anal. Calcd. for $C_{22}H_{39}N_5O_6Si_2$: C 50.26, H 7.48, N 13.33. Found: C 49.90, H 7.37, N 13.54.

2'-O-Phenoxythiocarbonyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)guanosine (131)

The conditions of Procedure B were applied to 1.05 g (2 mmol) of (130) using 30 ml of anhydrous CH_3CN, 500 mg (4 mmol) of DMAP and 400 µl (2.2 mmol) of PTC chloride (114). After the standard work-up procedure the residue was applied to a column of silica (20 g, 2 x 20 cm) using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from 95% EtOH gave 1.25 g (94%) of (131): mp 255-258°C; uv (EtOH) max 245 nm (ϵ 18,800), (0.1 N HCl) max 252 nm (ϵ 15,100), (0.1 N NaOH) max 257 nm (ϵ 14,600); M.S. m/z 661.2436 (3.8%, M^+ = 661.2414), 662.2465 (1.6, M^++1), 507.2347 (19%, M^+-OCSOϕ), 508.2375 (8.7%, M^+-HOCSOϕ), 464.1801 (12%, M^+-OCSOϕ-iPr); Anal. Calcd. for $C_{29}H_{43}N_5O_7Si_2S$: C 52.62, H 6.55, N 10.58, S 4.84. Found: C 52.33, H 6.52, N 10.61, S 4.86.

2'-Deoxyguanosine (11)

A 1.00 g (1.5 mmol) sample of (131) was subjected to the reduction conditions of Procedure C using 30 ml of toluene, 600 µl (2.25 mmol) of n-Bu_3SnH and 50 mg (0.3 mmol) of AIBN. The deblocking step of Procedure D was performed directly on the reaction solution. Solvents were evaporated and the residue was partitioned between ether and water. The aqueous phase was applied to a column of Dowex 1 X 2 (OH^-) resin (10 ml, 2 x 5 cm) and the resin was washed well with water. Elution was effected with 0.25 M tetraethylammonium bicarbonate (TEAB) buffer (pH = 9.0). After evaporation of the eluate *in vacuo* the residue was taken up in 10 ml of water and reevaporated. This procedure was repeated four times to remove residual TEAB. Crystallization of the residue from water gave 345 mg (85%) of (11): mp 251-252°C; M.S. m/z 249.0864 (0.76%, $M^+[C_{10}H_{13}N_5O_4]$-18 = 249.0853), 151.0498 (13%, B+H), 117.0553 (41%, sugar ion); (lit.[149] mp 250°C).

4-Amino-7-[3,5-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-D-ribofuranosyl]pyrrolo[2,3-d]pyrimidine (132) (3',5'-*O*-TPDStubercidin)

The conditions of Procedure A were followed using 266 mg (1 mmol) of dried tubercidin (54), 10 ml of anhydrous pyridine and 320 µl (1 mmol) of TPDSCl (95). After the standard work-up procedure, a small portion of the crude residue was chromatographed on a column of silica using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from CH_3CN gave (132) as colourless platelets with mp 238-242°C; uv (MeOH) max 270 nm (ε 10,800) and 227 nm (ε 20,000), min 245 nm (ε 3,800); (0.1 *N* HCl) max 270 nm (ε 10,000) and 227 nm (ε 21,300), min 245 nm (ε 3,400); (0.1 N NaOH) max 273 nm (ε 11,300) and 217 nm (ε 38,100), min 244 nm (ε 3,900); M.S. m/z 508.2547 (8.0%, $M^+[C_{23}H_{40}N_4O_5Si_2]$ = 508.2528), 509.2598 (7.4%, M^++1), 466.2031 (55%, M^++1-iPr), 465.1980 (60%, M^+-iPr), 163.0588 (100%, BHCHO), 134.0589 (38%, B+H).

2'-*O*-Phenoxythiocarbonyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)tubercidin (133)

The conditions of Procedure B were applied to the residue of crude (132) using 15 ml of anhydrous CH_3CN, 250 mg (2 mmol) of DMAP and 200 μl (1.1 mmol) of PTC chloride (114). After the standard work-up procedure a small sample of the crude residue was chromatographed on silica using chloroform and 2% methanol/chloroform as eluants. Evaporation of the eluate gave an oil with uv (MeOH) max 271 nm and 232 nm, min 245 nm; M.S. m/z 491.2460 (12%, M^+-OCSOϕ [$C_{23}H_{39}N_4O_4Si_2$] = 491.2562), 490.2415 (24%, M^+-HOCSOϕ), 448.1905 (3.1%, M^+-OCSOϕ-iPr), 447.1887 (6.7%, M^+-HOCSOϕ-iPr), 163.0620 (75%, BHCHO), 134.0593 (44%, B+H).

2'-Deoxy-3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)tubercidin (134)

The crude (133) was reduced according to Procedure C using 200 ml of distilled toluene, 32 mg (0.2 mmol) of AIBN, and 400 μl (1.5 mmol) of *n*-Bu_3SnH. An aliquot of the reaction solution was removed for characterization of (134). Solvent was evaporated *in vacuo* and the residue was chromatographed on silica using chloroform and 1.5% methanol/chloroform as eluants. Evaporation of the appropriate fractions gave an oil with uv (MeOH) max 271 nm and 227 nm, min 245 nm; 200 MHz nmr ($CDCl_3$, TMS) δ 1.05 (m, 28, iPr), 2.58 (m, 2, H-2', 2"), 3.88 (m, 1, H-4'), 4.02 (d of d, $J_{4'-5''}$ = 4.6 Hz, $J_{5''-5'}$ = 12.3 Hz, 1, H-5"), 4.10 (d of d, $J_{4'-5'}$ = 3.9 Hz, $J_{5'-5''}$ = 12.3 Hz, 1, H-5'), 4.86 ('q', J ~ 7.5 Hz, 1, H-3'), 5.55 (br s, 2, NH_2-4), 6.40 (d, J_{5-6} = 3.7 Hz, 1, H-5), 6.56 (d of d, $J_{1'-2'}$ = 4.5 Hz, $J_{1'-2''}$ = 6.5 Hz, 1, H-1'), 7.21 (d, $J_{5,6}$ = 3.7 Hz, 1, H-6), 8.30 (s, 1, H-2); M.S. m/z 492.2488 (13%, $M^+[C_{23}H_{40}N_4O_4Si_2]$ = 492.2467), 449.1923 (100%, M^+-iPr), 161.0820 (1.5%, BHCH=CH), 134.0941 (51%, B+H).

4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo-[2,3-d]pyrimidine (55) (2'-Deoxytubercidin)

The balance of the above reaction solution was subjected to deblocking Procedure D using 2 ml (2 mmol) of the 1 *M* *n*-Bu_4NF solution. Solvents were evaporated and the residue was partitioned between ether and water. The aqueous phase was applied to a column of Dowex 1 X 2 (OH^-) resin (10 ml, 1.5 x 10 cm). The resin was washed with water prior to elution of the product with 10% methanol/water. Evaporation of the eluant and crystallization of the residue from ethanol gave (55): mp 217-218.5°C; $[\alpha]_D^{24}$ -43.8 (*c* 0.34 MeOH); uv (MeOH) max 271 (ε 13,600) and 227 nm (ε 24,200), min 239 nm (ε 2,700); (0.1 *N* HCl) max 271 nm (ε 12,500) and 226 nm (ε 25,700), min 244 nm (ε 3,800); (0.1 *N* NaOH) max 271 nm (ε 13,100), min 239 nm (ε 3,100); M.S. m/z 250.1070 (5.0%, $M^+[C_{11}H_{14}N_4O_3]$ = 250.1066), 161.0826 (14%, $BHCH{=}CH_2$), 135.0637 (11%, B+2H), 134.0592 (100, B+H). *Anal*. Calcd. for $C_{11}H_{14}N_4O_3$: C 52.78, H 5.64, N 22.39. Found: C 52.48, H 5.62, N 22.31; (lit.[76] mp 217-218°C; $[\alpha]_D^{24}$ -43 (*c* 0.58 EtOH)).

Treatment of 1.064 g (4 mmol) of tubercidin (54) by the four step sequence (54→132→134→135→55) without purification of intermediates gave 680 mg (2.72 mmol) of recrystallized 2'-deoxytubercidin (55) in 68% overall yield.

4-Amino-5-cyano-7-[3,5-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-*D*-ribofuranosyl]pyrrolo[2,3-d]pyrimidine (136) (3',5'-*O*-TPDStoyocamycin)

The conditions of Procedure A were applied to 582 mg (2 mmol) of dried toyocamycin (135) using 30 ml of anhydrous pyridine and 650 ml (2 mmol) of TPDSCl (95). After the standard work-up procedure the residue was chromatographed on a column of silica (15 g, 2 x 15 cm) using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from CH_3CN gave 945 mg (89%) of (136): mp 171-172°C; uv (MeOH) max 280 nm (ε 17,400) and 232 nm (ε 11,900), min 247 nm (ε 4,700); (0.1 *N* HCl) max 274 nm (ε 13,100) and 235 nm (ε 17,900), min 249 nm (ε 5,000); (0.1 *N* NaOH) max 280 nm (ε 16,700) and 233 nm (ε 11,000), min 247 nm (ε 4,600); M.S. m/z 533.2478 (4.1%, $M^+[C_{24}H_{39}N_5O_5Si_2]$ = 533.2492), 534.2514 (1.7%, M^++1), 491.1960 (38%, M^++1-iPr), 490.1938 (100%, M^+-iPr), 188.0566 (18%, BHCHO), 159.0507 (10%, B+H); *Anal*. Calcd. for $C_{24}H_{39}N_5O_5Si_2$: C 54.04, H 7.37, N 13.13. Found: C 53.95, H 7.33, N 12.97.

2'-O-Phenoxythiocarbonyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)toyocamycin (137)

The conditions of Procedure B were applied to 800 mg (1.5 mmol) of (136) using 20 ml of anhydrous CH_3CN, 375 mg (3.0 mmol) of DMAP and 300 µl (1.6 mmol) of PTC chloride (114). After the standard work-up procedure a portion of the residue was chromatographed on a column of silica using chloroform and 1.5% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from ethanol gave (137): mp 136-139°C; uv (MeOH) max 278 nm (ε 16,600) and 230 nm (ε 17,000), min 250 nm (ε 8,400); (0.1 N HCl) max 272 nm (ε 13,200) and 233 nm (ε 21,100), min 250 nm (ε 7,900), (0.1 N NaOH) max 279 nm (ε 16,800) and 233 nm (ε 21,800), min 253 nm (ε 7,400); M.S. m/z 626.1904 (11%, M^+-iPr = 626.1925), 516.2407 (46%, M^+-OCSOϕ), 515.2379 (100%, M^+-HOCSOϕ), 472.1833 (11%, M^+-iPr-HOCSOϕ), 159.0544 (9.6%, B+H); Anal. Calcd. for $C_{31}H_{43}N_5O_6Si_2S$: C 55.59, H 6.47, N 10.46, S 4.79. Found: C 55.20, H 6.49, N 10.74, S 4.65.

2'-Deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)toyocamycin (138)

The reduction conditions of Procedure C were applied to the crude residue of (137) using 30 ml of toluene, 600 µl (2.2 mmol) of n-Bu_3SnH and 45 mg (0.3 mmol) of

AIBN. After the standard work-up procedure the residue was chromatographed on a column of silica (10 g, 2 x 10 cm) using chloroform and 1.5% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from CH_3CN gave 675 mg (87%) of (138): mp 174-177°C; uv (MeOH) max 279 nm (ε 16,400) and 230 nm (ε 11,700), min 246 nm (ε 4,000); (0.1 N HCl) max 275 nm (ε 13,100) and 232 nm (ε 18,100), min 248 nm (ε 5,000); (0.1 N NaOH) max 279 nm (ε 15,700) and 233 nm (ε 10,300), min 246 nm (ε 4,400); 200 MHz nmr ($CDCl_3$, TMS) δ 1.05 (m, 28, iPr), 2.43 (d of d of d, $J_{2''-1'}$ = 2.0 Hz, $J_{2''-2'}$ = 13.0 Hz, $J_{2''-3'}$ = 7.2 Hz, 1, H-2"), 2.62 (d of d of d, $J_{2'-1'}$ = 6.8 Hz, $J_{2'-2''}$ = 13.0 Hz, $J_{2'-3'}$ = 9.8 Hz, 1, H-2'), 3.84 (d of t, $J_{4'-3'}$ = 8.0 Hz, $J_{4'-5'}$ = $J_{4'-5''}$ = 3.0 Hz, 1, H-4'), 4.03 (d of d, $J_{5''-4'}$ = 3.0 Hz, $J_{5''-5'}$ = 12.7 Hz, 1, H-5"), 4.15 ($J_{5'-4'}$ = 3.0 Hz, $J_{5'-5''}$ = 12.7 Hz, 1, H-5'), 4.68 (m, 1, H-3'), 5.63 (s, 2, NH_2-4), 6.43 (d of d, $J_{1'-2''}$ = 2.0 Hz, $J_{1'-2'}$ = 6.8 Hz, 1, H-1'), 7.94 (s, 1, H-6), 8.34 (s, 1, H-2); M.S. m/z 517.2548 (6.4%, $M^+[C_{24}H_{39}N_5O_4Si_2]$ = 517.2543), 518.2568 (2.8%, M^++1), 474.2001 (M^+-iPr), 159.0535 (17%, B+H); Anal. Calcd. for $C_{24}H_{39}N_5O_4Si_2$: C 55.69, H 7.59, N 13.53. Found: C 55.76, H 7.55 N 13.78.

4-Amino-5-cyano-7-(2-deoxy-β-D-erythro-pentofuranosyl)-pyrrolo[2,3-d]pyrimidine (139) (2'-Deoxytoyocamycin)

Procedure D was applied to 517 mg (1 mmol) of (138) dissolved in 20 ml of toluene using 2 ml of *n*-Bu$_4$NF solution (1 *M* in THF) and stirring at 80°C for 2 h. Solvents were evaporated *in vacuo* and the residue was partitioned between ether and water. The aqueous phase was applied to a column of carbon (2 g, 1 x 5 cm) and the carbon was washed with 50 ml water and then 50 ml ethanol. Washing was continued with chloroform and a 20% solution of benzene in chloroform was required for elution of the product. Evaporation of the appropriate fractions and crystallization of the residue from ethanol/ether gave 245 mg (89%) of (*139*): mp 208-209°C; $[\alpha]_D^{24}$ -24.6 (*c* 0.28 MeOH); uv (MeOH) max 278 nm (ε 15,700) and 229 nm (ε 12,700), min 247 nm (ε 4,700) and 221 nm (ε 11,800); (0.1 *N* HCl) max 273 nm (ε 12,400) and 231 nm (ε 17,600), min 247 nm (ε 5,200); (0.1 *N* NaOH) max 278 nm (ε 15,100) and 231 nm (ε 12,000), min 246 (ε 4,800); 200 MHz nmr (DMSO-*d*$_6$, TMS) δ 2.28 (d of d of d, $J_{2''-2'}$ = 13.1 Hz, $J_{2''-1'}$ = 6.1 Hz, $J_{2''-3'}$ = 3.2 Hz, 1, H-2"), 2.48 (d of d of d, $J_{2'-1'}$ = 7.2 Hz, $J_{2'-2''}$ = 13.1 Hz, $J_{2'-3'}$ = 5.8 Hz, 1, H-2'), 3.58 (m, 2, H-5', H-5"), 3.87 (m, 1, H-4'), 4.38 (m, 1, H-3'), 5.06 (t, $J_{5',5''-OH-5'}$ = 5.5 Hz, 1, OH-5'), 5.32 (d, $J_{3'-OH-3'}$ = 4.1 Hz, 1, OH-3'), 6.53 (d of d, $J_{1'-2'}$ = 7.2 Hz, $J_{1'-2''}$ = 6.1 Hz, 1, H-1'), 6.88 (br s, 2, NH$_2$-4), 8.26 (s, 1, H-6), 8.44 (s, 1, H-2); M.S. m/z 275.1020 (6.6%, $M^+[C_{12}H_{13}N_5O_3]$ = 275.1012), 245.0933 (2.2%, M^+-CH_2O), 186.0780 (21%, $BHCH=CH_2$), 160.0592 (18%, B+2H), 159.0544 (100%, B+H); *Anal*. Calcd. for $C_{12}H_{13}N_5O_3$: C 52.34, H 4.76, N 25.45. Found: C 52.42, H 4.83, N 25.16.

4-Amino-5-carboxamido-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-d]pyrimidine (141) (2'-Deoxysangivamycin)

A 550 mg (2 mmol) sample of (139) was applied to a column of Dowex 1 X 2 (OH^-) resin (2 x 10 cm). The resin was washed with 200 ml of water and then with a mixture of methanol-water (1:9). The ratio of methanol in water was gradually increased to 2:3 which eluted the product. Evaporation of the eluate and crystallization of the residue from ethanol gave 551 mg (94%) of (141): mp 272-275°C; $[\alpha]_D^{24}$ = -22.3 (*c* 0.26 MeOH); uv (MeOH) max 279 nm (ε 14,800) and 231 nm (ε 10,200), min 255 nm (ε 6,500); (0.1 *N* HCl) max 274 nm (ε 12,500) and 230 nm (ε 14,400), min 253 nm (ε 6,900); (0.1 *N* NaOH) max 278 nm (ε 14,800), min 255 nm (ε 7,400); 200 MHz nmr (DMSO-d_6, TMS) δ 2.27 (d of d of d, $J_{2''-1'}$ = 6.1 Hz, $J_{2''-2'}$ = 12.9 Hz, $J_{2''-3'}$ = 3.4 Hz, 1, H-2"), 2.42 (d of d of d, $J_{2'-1'}$ = 7.5 Hz, $J_{2'-2''}$ = 12.9 Hz, $J_{2'-3'}$ = 5.8 Hz, 1, H-2'), 3.56 (m, 2, H-5",5"), 3.86 (m, 1, H-4'), 4.39 (m, 1, H-3'), 5.00 (t, $J_{5',5''-OH-5'}$ = 5.7 Hz, 1, OH-5'), 5.31 (d, $J_{3'-OH-3'}$ = 4.4 Hz, 1, OH-3') 6.53 (d of d, $J_{1'-2'}$ = 7.5 Hz, $J_{1'-2''}$ = 6.1 Hz, 1, H-1'), 7.36 (br s, 2, NH_2-4) 7.94 (br s, 2, $CONH_2$), 8.1 (s, 1, H-6), 8.15 (s, 1, H-2); M.S. m/z 293.1128 (5.9%, $M^+[C_{12}H_{15}N_5O_4]$ = 293.1124), 204.0886 (12%, BHCH=CH_2), 177.0649 (100%, B+H), 176.0573 (1.6%, B); *Anal*. Calcd. for $C_{12}H_{15}N_5O_4$: C

49.15, H 5.11, N 25.44. Found: C 48.95, H 5.11, N 25.55.

3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-cytidine (142)

The conditions of Procedure A were applied to 972 mg (4 mmol) of dried cytidine (8) using 50 ml of anhydrous pyridine and 1.3 ml (4 mmol) of TPDSCl (95). After the standard work-up procedure crystallization of the residue from chloroform gave 1.77 g (91%) of (142) mp 267-269°C; uv (MeOH) max 273 nm (ε 8,800) min 250 nm (ε 6,100), (0.1 N HCl) max 280 nm (ε 13,100) min 240 nm (ε 1,400), (0.1 N NaOH) max 271 nm (ε 8,800), min 250 nm (ε 6,100); M.S. m/z 485.2384 (12%, $M^+[C_{21}H_{39}N_3O_6Si_2]$ = 485.2379), 486.2399 (5.6%, M^++1), 442.1833 (96%, M^+-iPr), 443.1853 (28%, M^++1-iPr), 140.0460 (10%, BHCHO), 112.0512 (100%, B+2H); Anal. Calcd. for $C_{21}H_{39}N_3O_6Si_2$: C 51.94, H 8.10, N 8.65. Found: C 52.20, H 8.07, N 8.52.

4-N-Acetyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine (144)

The conditions of Procedure A were applied to 570 mg (2 mmol) of 4-N-acetylcytidine[125] (143) using 25 ml of anhydrous pyridine and 650 μl (2 mmol) of TPDSCl (95). After the standard work-up procedure crystallization of the residue from ethanol gave 975 mg (92%) of (144); mp 111-113°C; uv (MeOH) max 297 nm (ε 8,200) and 247 nm (ε 15,000), min 270 nm (ε 4,200); (0.1 N HCl) max 305 nm (ε 11,200) and 243 nm (ε 10,300), min 268 nm (ε 3,600); M.S. m/z 527.2524 (0.3%, $M^+[C_{23}H_{41}N_3O_7Si_2]$ = 527.2533); 484.2006 (7.4%, M^+-iPr), 153.0535 (1.0%, B+H).

2'-O-Phenoxythiocarbonyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine (146)

To 970 mg (2 mmol) of (142) suspended in 100 ml of anhydrous CH_3CN was added 1.5 g (12 mmol) of DMAP and 800 µl (3.3 mmol) of PTC chloride (114). The resulting solution was stirred for 1 h. before 2 ml of water was added and the solvent was evaporated *in vacuo*. After the standard work-up procedure the residue was chromatographed on a column of silica (20 g, 2 x 20 cm) using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions gave 700 mg (55%) of (146) as an oil with uv (MeOH) max 273 and 233 nm, min 250 nm; M.S. m/z 425.1615 (27%, M^+-iPr-OCSOϕ), 424.1723 (26%, M^+-iPr-HOCSOϕ), 141.0667 (24%, BCHO+2H), 111.0432 (8.2%, B+H).

4-N-Acetyl-2'-O-phenoxythiocarbonyl-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine (147)

To 970 g (2 mmol) of (142) suspended in 100 ml of anhydrous CH_3CN was added 1.5 g (12 mmol) of DMAP and 800 μl (4.4 mmol) of PTC chloride (114). The resulting solution was stirred for 1 h before 1 ml (10 mmol) of acetic anhydride was added. After 30 min solvents were evaporated and the residue was subjected to the standard work-up procedure and then chromatographed on a column of silica (10 g, 2 x 10 cm) using chloroform and 1% chloroform/methanol as eluants. Evaporation of the appropriate fractions gave 645 mg (49%) of (147) as an oil with uv (MeOH) max 298, 234 nm, min 270 nm; M.S. m/z 467.1835 (3.9%, M^+-iPr-OCSOϕ), 466.1841 (10%, M^+-iPr-HOCSOϕ), 183.5327 (7.9%, BCHO+2H).

4-N-Acetyl-2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine (148)

The conditions of Procedure C were applied to 600 mg (0.9 mmol) of (147) using 15 ml of toluene, 360 μl (1.3 mmol) of n-Bu_3SnH and 30 mg (0.2 mmol) of AIBN. Solvents were removed in vacuo and the residue was chromatographed on a column of silica (10 g, 2 x 10 cm) to give 400 mg (87%) of (148) as an oil with uv(MeOH) max 298 nm; 200 MHz nmr($CDCl_3$, TMS) δ 1.05 (m, 28, iPr), 2.36 (d of d, $J_{2''-2'}$ = 13.5 Hz, $J_{2''-3'}$ = 7.5 Hz, 1, H-2"), 2.60 (d of d of d, $J_{2'-1'}$ = 6.9 Hz, $J_{2'-2''}$ = 13.5 Hz, $J_{2'-3'}$ = 10.9 Hz, 1, H-2'), 3.83 (m, 1, H-4'), 4.03 (d of d, $J_{5''-5'}$ = 13.2 Hz, $J_{5''-4'}$ = 2.6 Hz, 1, H-5"), 4.22 (d of d,

$J_{5'-5''}$ = 13.2 Hz, $J_{5''-4'}$ ~ 1.5 Hz, 1, H-5'), 4.37 (m, 1, H-3'), 6.07 (d, $J_{1'-2'}$ = 6.9 Hz, 1, H-1'), 7.43 (d, J_{5-6} = 7.8 Hz, 1, H-5), 8.28 (d, J_{5-6} = 7.8 Hz, 1, H-6); M.S. m/z 511.2524 (0.25%, $M^+[C_{23}H_{41}N_3O_6Si_2]$ = 511.2533), 468.2001 (9.2%, M^+-iPr), 153.0535 (1.0%, B+H).

2'-Deoxycytidine (12)

To 350 mg (0.68 mmol) of (148) dissolved in 5 ml of tetrahydrofuran (THF) was added 2 ml (2 mmol) of a 1 M n-Bu_4NF solution in THF and the solution was heated to reflux for 1 h. Solvents were removed *in vacuo* and the residue was treated with 1 N NaOMe in methanol for 0.5 h at 40°C. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ether and water. The aqueous phase was applied to a column of Dowex 1 X 2 (OH^-) resin. Elution of the product with water, evaporation and crystallization of the residue from ethanol gave 130 mg (85%) of (12): mp 200-201°C; M.S. m/z 227.0906 (1.8%, $M^+[C_9H_{13}N_3O_4]$ = 227.0907), 138.0668 (18%, $BHCH{=}CH_2$), 111.0436 (100%, BH); (lit.[149] mp 200-201°C).

Methyl 3,5-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-D-ribofuranoside (150)

The conditions of Procedure A were applied to 164 mg (1 mmol) of Methyl β-D-ribofuranoside (149) using

10 ml of anhydrous pyridine and 320 µl (1 mmol) of TPDSCl (95). The standard work-up procedure was followed (excluding the acid wash) and the crude residue was chromatographed on ammonia impregnated silica (10 g, 2 x 10 cm). The column was run quickly (to reduce hydrolysis) using Skelly B and chloroform as eluants. Evaporation of the appropriate fractions gave 325 mg (80%) of (150) as an oil. M.S. m/z 363.1686 (3.5%, M^+-iPr[$C_{15}H_{31}O_6Si_2$] = 363.1661), 332.1426 (3.5%, M^+-iPr-OCH_3), 331.1404 (9.6%, M^+-iPr-CH_3OH).

Methyl 2-O-phenoxythiocarbonyl-3,5-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-D-ribofuranoside (151)

The conditions of Procedure B were applied to 300 mg (0.76 mmol) of (150) using 15 ml of anhydrous acetonitrile, 200 mg (1.5 mmol) of DMAP and 150 µl (0.80 mmol) of PTC chloride (114). The standard work-up procedure was followed (excluding the acid wash as in the previous reaction) and the residue was chromatographed on ammonia impregnated silica (10 g, 2 x 10 cm) using Skelly B and 1:1 Skelly B/chloroform as eluants. Evaporation of the appropriate fractions gave 300 mg (75%) of (151) as an oil. M.S. m/z 390.2275 (2.1%, M^+-OCSOϕ[$C_{18}H_{38}O_5Si_2$] = 390.2259), 359.2086 (9.2%, M^+-OCSOϕ-OMe), 316.1431 (26%, M^+-OCSOϕ-OMe-iPr).

Methyl 3,5-di-O-p-toluyl-β-D-erythro-pentofuranoside (152)

To 270 mg (0.5 mmol) of (151) dissolved in 10 ml of toluene was added 200 μl (0.75 mmol) of n-Bu_3SnH and 15 mg (0.1 mmol) of AIBN. The reduction was carried out following Procedure C. The reaction was subjected to the deblocking step of Procedure D upon completion. The solvent was evaporated in vacuo and the residue was partitioned between ether/water. The aqueous phase was evaporated to dryness and co-evaporated several times with pyridine before it was dissolved in 15 ml of anhydrous pyridine. A 5-fold molar excess of p-toluyl chloride was added to the stirred solution at room temperature. After 3 h the solvent was evaporated in vacuo and the residue was partitioned between ether and water. The organic phase was washed with 2 x 10 ml of H_2O, saturated $NaHCO_3/H_2O$, saturated $NaCl/H_2O$, dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed on a column of silica (CC-7, 5 g, 1.5 x 7 cm) using Skelly B and 10% ether/Skelly B as eluants. Evaporation of the appropriate fractions and crystallization of the residue from ethanol gave 120 mg (60%) of (152): mp 76-78°C; $[\alpha]_D^{25}$ -9.4 (c 1.0, $CHCl_3$); [(lit.[150] m.p. 76.5-78°C; $[\alpha]_D^{20}$ -8.1° (c 2.5, $CHCl_3$)].

Treatment of 328 mg (2 mmol) of Methyl β-D-ribofuranoside (149) by the five step sequence (149→150→151→152) without isolation of intermediates gave 445 mg of (152) in 58% overall yield.

1,2;5,6-di-*O*-isopropylidene-3-*O*-phenoxythiocarbonyl-α-*D*-glucofuranose (154)

The conditions of Procedure B were applied to 260 mg (1 mmol) of 1,2;5,6-di-*O*-isopropylideneglucose (153) using 15 ml of acetonitrile and 200 μl (1.1 mmol) of PTC chloride (114). After the standard work-up procedure the residue was purified on a column of silica (10 g, 2 x 10 cm) using chloroform as the eluant. Evaporation of the appropriate fractions and crystallization of the residue from aqueous methanol gave 340 mg (86%) of (154): mp 108-110°C; 100 MHz nmr ($CDCl_3$, TMS) δ 1.30-1.50 (4 x s, 12, Me), 4.10 (m, 2, H-6, H-6'), 4.30 (m, 2, H-4, H-5), 4.82 (d, J_{1-2} = 3.8 Hz, 1, H-2), 5.70 (m, 1, H-3), 6.00 (d, $J_{1,2}$ = 3.8 Hz, 1, H-1), ~7.3 (m, 5, phenyl H's); M.S. m/z 396.1251 (0.25%, $M^+[C_{19}H_{24}O_7S]$ = 396.1230), 381.1010 (23%, M^+-CH_3), 243.1241 (20%, M^+-OCSOϕ), 185.0816 (21%, M^+-OCSOϕ-CH_3COCH_3); *Anal*. Calcd. for $C_{19}H_{24}O_7S$: C 57.56, H 6.10, S 8.09. Found: C 57.71, H 6.00, S 8.06.

3-Deoxy-1,2;5,6-di-*O*-isopropylidene-α-*D*-*ribo*-hexofuranose (155)

The reducing conditions of Procedure C were applied to 792 mg (2 mmol) of (154) dissolved in 30 ml of toluene using 800 μl (3 mmol) of *n*-Bu_3SnH and 64 mg (0.4 mmol) of AIBN. Solvents were removed *in vacuo* and the residue was purified on a column of silica (10 g, 2 x 10 cm) using Skelly B as the eluant. Concentration of the appropriate fractions gave 425 mg (87%) of (155) as an oil; 100 MHz nmr ($CDCl_3$, TMS) δ~1.4 (4 x s, 12, CH_3), 1.78 (m, 1, H-3'), 2.20 (d of d, $J_{3-3'}$ = 13.0 Hz, J_{2-3} = 4.0 Hz, 1, H-3), 3.80 (m, 1, H-5), 4.10 (m, 3, H-4, H-6, H-6'), 4.75 (t, J_{1-2} = $J_{2-3'}$ = 4.0 Hz, 1, H-2), 5.78 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1); M.S. m/z 229 (47%, M^+-CH_3), 186 (1.2%, $M^+-CH_3COCH_3$); Anal. Calcd. for $C_{12}H_{20}O_5$: C 59.00, H 8.25. Found: C 59.30, H 8.25.

Treatment of 520 mg (2 mmol) of (153) by the two step sequence without isolation of (154) gave 415 mg of (155) in 85% overall yield.

9-[3,5-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-β-D-ribofuranosyl]purin-6-one (166) (3',5'-O-TPDSinosine)

The conditions of Procedure A were applied to 134 mg (0.5 mmol) of dried inosine (165) using 10 ml of anhydrous pyridine and 160 µl (0.5 mmol) of TPDSCl (95). After the standard work-up procedure the residue was chromatographed on a column of silica (5 g, 1 x 10 cm) using chloroform and 5% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from 1:1 acetonitrile/ethanol gave 220 mg (86%) of (166): mp 219-220.5°C; uv (MeOH) max 249 nm (ε 12,100); (0.1 N HCl) max 251 nm (ε 10,700);

(0.1 *N* NaOH) max 253 nm (ε 13,000); M.S. m/z 510.2331 (4.0%, $M^+[C_{22}H_{38}N_4O_6Si_2]$ = 510.2328), 467.1774 (100%, M^+-iPr), 136.0359 (30%, B+H); *Anal*. Calcd. for $C_{22}H_{38}N_4O_6Si_2$: C 51.81, H 7.51, N 10.98. Found: C 51.86, H 7.45, N 10.84.

7-Amino-3-[3,5-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-β-*D*-ribofuranosyl]pyrazolo[4,3-d]pyrimidine (*176*) (3',5'-*O*-TPDSformycin)

The conditions of Procedure A were followed using 267 mg (1 mmol) of dried formycin (*175*), 15 ml of anhydrous pyridine and 320 µl (1 mmol) of TPDSCl (*95*). After the standard work-up procedure the crude residue was chromatographed on silica using chloroform and 2% methanol/chloroform as eluants. Evaporation of the appropriate fractions and crystallization of the residue from CH_3CN gave 428 mg of (*176*): mp 149-151°C; uv (MeOH) max 294 nm (ε 10,300), (sh) 304 nm (ε 6,900), (sh) 287 nm (ε 9,400); (0.1 *N* HCl) max 295 nm (ε 10,700) and 232 nm (ε 8,800), min 266 nm (ε 4,400) and 222 nm (ε 2,900); (0.1 *N* NaOH) max 304 nm (ε 7,500) and 234 nm (ε 16,400), min 267 nm (ε 3,100) and 223 nm (ε 10,500); M.S. m/z 509.2479 (14%, $M^+[C_{22}H_{39}N_5O_5Si_2]$ = 509.2480), 510.2526 (10%, M^++1), 466.1936 (100%, M^+-iPr), 178.0722 (18%, $BHCH_2CHO$), 164.0561 (65%, BHCHO).

Procedure A was applied to the following nucleosides on a 0.1 mmol scale using 2.5 ml of pyridine and 32 µl (0.1 mml) of TPDSCl (95). The standard work-up procedure was followed and the residues were chromatographed on silica plates (5 x 20 cm) using 5% methanol/chloroform as eluant. The silica which contained the product was scraped off the plate and eluted with 7% methanol/chloroform. Evaporation of the eluate gave an oil in each case.

2,6-Diamino-9-β-D-ribofuranosylpurine (167)
5-β-D-Ribofuranosyluracil (169) (pseudouridine)
4-Hydroxy-1-β-D-ribofuranosylpyridin-2-one (171)
    (3-deazauridine)
4-Amino-1-β-D-ribofuranosylpyridin-2-one (173) (3-
    deazacytidine)
5(3)-Carboxamido-4-hydroxy-3(5)-β-D-ribofuranosylpyrazole
    (177) (pyrazomycin)
9-α-D-Ribofuranosyladenine (179) (α-adenosine)
1-α-D-Ribofuranosyluracil (181) (α-uridine)
1-α-D-Ribofuranosylcytosine (183) (α-cytidine)
9-β-D-Arabinofuranosyladenine (159)
1-β-D-Arabinofuranosylcytosine (189)
9-(2-Chloro-2-deoxy-β-D-arabinofuranosyl)adenine (156)
9-(2-Azido-2-deoxy-β-D-arabinofuranosyl)adenine (187)
9-α-D-Arabinofuranosyladenine (185)

3',5'-O-(1,1,3,3-Tetraisopropyldisilox-1,3-diyl)-nucleosides (3',5'-O-TPDSnucleosides)

2,6-Diamino-9-(3,5-O-TPDS-β-D-ribofuranosyl)purine (168)

The residue obtained was crystallized from ethanol to give white needles with mp 190-192°C; uv (MeOH) max 280 nm (ε 10,700), 258 nm (ε 9,900) and 217 nm (ε 25,200), min 268 nm (ε 8,400) and 235 nm (ε 4,200); (0.1 N HCl) max 292 nm (ε 8,800), 252 nm (ε 10,300) and 214 nm (ε 15,500), min 270 nm (ε 5,200) and 237 nm (ε 5,100), (0.1 N NaOH) max 280 nm (ε 10,800) and 256 nm (ε 9,900), min 265 nm (ε 8,100) and 239 nm (ε 6,600); M.S. m/z 524.2598 (18%, $M^+[C_{22}H_{40}N_6O_5Si_2]$ = 524.2599), 481.2053 (16%, M^+-iPr), 150.0654 (53%, B+H).

3',5'-O-TPDSpseudouridine (170)

Uv (MeOH) max 260 nm; M.S. m/z 443.1677 (9.5%, M^+-iPr$[C_{18}H_{31}N_2O_7Si_2]$ = 443.1662), 141.0350 (100%, BHCHO).

3',5'-O-TPDS-3-deazauridine (172)

Uv (MeOH) max 280 nm; M.S. m/z 485.2262 (12%, $M^+[C_{22}H_{39}NO_7Si_2]$ = 485.2265), 442.1718 (100%, M^+-iPr), 112.0398 (83%, B+2H), 111.0317 (12%, B+H).

3',5'-O-TPDS-3-deazacytidine (174)

Uv (MeOH) max 262 nm; M.S. m/z 484.2429 (1.8%, $M^+[C_{22}H_{40}N_2O_6Si_2]$ = 484.2424), 485.2481 (3%, M^++1), 441.1870 (10%, M^+-iPr), 442.1927 (19%, M^++1-iPr), 139.0503 (5.4%, BHCHO), 111.0557 (53%, B+2H).

3',5'-O-TPDSpyrazomycin (178)

Uv (MeOH) max 266 nm; M.S. m/z 458.1775 (13%, M^+-iPr[$C_{18}H_{32}N_3O_7Si_2$] = 458.1779), 170.0565 (19%, $BHCH_2CHO$), 156.0414 (2.3%, BHCHO).

3',5'-O-TPDS-α-adenosine (180)

Uv (MeOH) max 260 nm; M.S. m/z 509.2489 (6.1%, M^+[$C_{22}H_{39}N_5O_5Si_2$] = 509.2489), 466.1942 (100%, M^+-iPr), 178.0728 (5.0%, $BHCH_2CHO$), 164.0573 (23%, BHCHO), 136.0623 (17%, B+2H), 135.0546 (4.9%, B+H).

3',5'-O-TPDS-α-uridine (182)

Uv (MeOH) max 262 nm; M.S. m/z 443.1677 (67%, M^+-iPr[$C_{18}H_{31}N_2O_7Si_2$] = 443.1670), 444.1728 (100%, M^++1-iPr), 155.0415 (3.2%, $BHCH_2CHO$), 113.0354 (3.7%, B+2H), 112.0278 (1.1%, B+H).

3',5'-O-TPDS-α-cytidine (184)

Uv (MeOH) max 270 nm; M.S. m/z 485.2380 (9.0%, M^+[$C_2H_{39}N_3O_6Si_2$] = 485.2378), 486.2398 (4.3%, M^++1), 442.1832 (100%, M^+-iPr), 140.0462 (8.7%, BHCHO), 112.0512 (95%, B+2H).

9-(3,5-O-TPDS-β-D-arabinofuranosyl)adenine (160)

Uv (MeOH) max 260 nm; M.S. m/z 509.2483 (5.2%,

$M^+[C_{22}H_{39}N_5O_5Si_2]$ = 509.2490), 466.1927 (100%, M^+-iPr), 164.0573 (11%, BHCHO), 136.0621 (19%, B+2H), 135.0545 (3.6%, B+H).

1-(3,5-O-TPDS-β-D-arabinofuranosyl)cytosine (190)

Uv (MeOH) Max 270 nm; M.S. m/z 485.2386 (1.0%, $M^+[C_{21}H_{39}N_3O_6Si_2]$ = 485.2378), 442.1832 (10%, M^+-iPr), 140.0463 (1.1%, BHCHO), 112.0465 (11%, B+2H), 111.0433 (100%, B+H).

9-(2-Chloro-2-deoxy-3,5-O-TPDS-β-D-arabinofuranosyl)-adenine (164)

Uv (MeOH) max 259 nm; M.S. m/z 527.2170 (8.0%, $M^+[C_{22}H_{38}N_5O_4Si_2Cl]$ = 527.2167), 529.2160 (2.6%, M^++2), 484.1612 (100%, M^+-iPr), 486.1603 (33%, M^++2-iPr), 164.0574 (10%, BHCHO), 136.0625 (17%, B+2H).

9-(2-Azido-2-deoxy-3,5-O-TPDS-β-D-arabinofuranosyl)-adenine (188)

Uv (MeOH) max 261 nm; M.S. m/z 534.2521 (2.9%, $M^+[C_{22}H_{38}N_8O_4Si_2]$ = 534.2557), 536.2642 (9.0%, M^++2), 535.2590 (9.9%, M^++1), 493.2129 (79%, M^++2-iPr), 492.2074 (85%, M^++1-iPr), 491.2008 (30%, M^+-iPr), 463.1982 (1.6%, M^+-N_2-iPr), 164.0573 (29%, BHCHO).

9-(3,5-O-TPDS-α-D-arabinofuranosyl)adenine (186)

Uv (MeOH) max 260 nm; M.S. m/z 509.2484 (2.0%, $M^+[C_{22}H_{39}N_5O_5Si_2]$ = 509.2490), 467.1974 (42%, M^++1-iPr), 466.1945 (100%, M^+-iPr), 164.0573 (15%, BHCHO), 136.0622 (62%, B+2H), 135.0546 (6.7%, B+H).

6-N-Acetyl-9-(2-O-acetyl-3,5-O-TPDS-β-D-arabinofuranosyl)adenine (162)

Procedure A was followed using 27 mg (0.1 mmol) of 9-β-D-Arabinofuranosyladenine (159), 5.0 ml of pyridine and 32 µl (0.1 mmol) of TPDSCl (95). After a 3 h period, 20 µl (2 mmol) of acetic anhydride was added to the reaction solution and stirring was continued for 4 h. Solvents were evaporated and the residue was chromatographed on a column of silica (6 g, 1.5 x 7 cm) using chloroform as the eluant. Evaporation of the appropriate fractions gave 45 mg (82%) of (162) as an oil with uv (MeOH) 271 nm; M.S. m/z 593.2704 (2.3%, $M^+[C_{26}H_{43}N_5O_7Si_2]$ = 593.2701), 550.2150 (100%, M^+-iPr), 509.2076 (15%, M^+-iPr-OAc), 508.2065 (38%, M^+-iPr-HOAc), 261.1710 (8.1%, BHCH=CHOAc), 178.0725 (17%, B+2H), 179.0646 (3.6%, B+H).

6-N-Acetyl-9-(2-O-acetyl-3,5-O-TPDS-α-D-arabinofuranosyl)adenine (191)

The procedure outlined above was applied to 27 mg (0.1 mmol) of 9-α-D-arabinofuranosyladenine (185) using 5.0 ml of pyridine, 32 µl (0.1 mmol) of TPDSCl (95) and 20 µl (2 mmol) of acetic anhydride. A 46 mg (84%)

yield of (191) was obtained as an oil with uv (MeOH) max 271 nm; 200 MHz nmr (DMSO-d_6, TMS) δ~1.05 (m, 28, iPr H's), 2.03 (s, 3, 6-*N*-COCH$_3$), 2.28 (s, 3, 2'-*O*-COCH$_3$), 3.98 (m, 2, H-5', H-5"), 4.61 (m, 2, H-3', H-4'), 6.20 (d, $J_{H-1'-H-2'}$ = 5.8 Hz, 1, H-1'), 6.26 (m, 1, H-2'), 8.64, 8.69 (2 x s, 2, H-2, H-8), 10.72 (s, 1, 6-N-H); M.S. m/z 593.2690 (1.0%, M$^+$[$C_{26}H_{43}N_5O_7Si_2$] = 593.2701), 550.2151 (100%, M$^+$-iPr), 509.2078 (21%, M$^+$=iPr-OAc), 508.2057 (58%, M$^+$-iPr-HOAc), 261.1705 (12%, BHCH=CHOAc), 178.0727 (13%, B+2H), 177.0653 (2.7% B+H).

2-Deutero-2'-deoxyadenosines (157a, 157b)

a) The reduction of a 65 mg (0.1 mmol) sample of (125) was carried out as described for (127) substituting *n*-Bu$_3$SnD for *n*-Bu$_3$SnH. The product obtained showed the identical chromatographic mobility of (127). The deblocking procedure described for (10) was applied directly to the reduction solution and the analogous work-up was continued to give 22.5 mg (90%) of (157a, 157b) as an oil. 400 MHz nmr (DMSO-d_6, TMS) δ 2.30 (d of d, $J_{2"-1'}$ = 2.8 Hz, $J_{2"-3'}$ = 5.8 Hz, ~0.12, H-2" of 157b), 2.71 (d of d, $J_{2'-1'}$ = 7.5 Hz, $J_{2'-3'}$ = 5.8 Hz, ~0.88, H-2' of 157a), 3.57 (d of d, $J_{5"-4'}$ = 4.2 Hz, $J_{5"-5'}$ = 12.0 Hz, 1, H-5"), 3.68 (d of d, $J_{5'-4'}$ = 4.2 Hz, $J_{5"-5'}$ = 12.0 Hz, 1, H-5'), 3.94 (m, 1, H-4'), 4.46 (d of d, $J_{3'-4'}$ = 2.8 Hz, $J_{3'-2'}$ = 5.8 Hz, 1, H-3'), 5.35 (m, 2, 3' and 5' OH), 6.39 (d, $J_{1'-2'}$ = 7.5 Hz, 1, H-1'), 7.29 (s, 2, 6-NH_2), 8.18 (s, 1, H-2), 8.36 (s, 1, H-8); M.S. m/z 252.1075 (6.7%, $M^+[C_{10}H_{12}DN_5O_3]$ = 252.1082), 163.0835 (67%, BHCH=CHD), 135.0662 (100%, B+H).

b) The four step sequence outlined in a) for the 2'-deoxygenation of adenosine was applied to 53 mg (0.2 mmol) of 9-β-D-arabinofuranosyladenine (159) without purification of the intermediates. A 34 mg (68%) yield of the 2'-deoxy-2'-deutero-adenosines (157a, 157b) was obtained as an oil.

c) A 53 mg (0.1 mmol) sample of 9-(2-chloro-2-deoxy-3,5-O-TPDS-β-D-arabinofuranosyl)adenine (164) was subjected to the reduction conditions of Procedure C using 10 ml of toluene, 40 µl (0.15 mmol) of n-Bu_3SnD, and 5 mg of AIBN. Deblocking via Procedure D was performed directly on the reaction solution using 250 µl of n-Bu_4NF (as a 1 M solution in THF). A 22 mg (88%) yield of (157a, 157b) was obtained as an oil. The spectral data for the mixture of (157a, 157b) obtained via b) or c) corresponded exactly to those of the mixture of (157a, 157b) from procedure a) above.

Methyl 3,5-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-α-D-ribofuranoside (193)

The procedure outlined for the synthesis of (150) was applied to 33 mg (0.2 mmol) of methyl α-D-ribofuranoside (192). An 81% (64 mg) yield of (193) was obtained as an oil. M.S. m/z 363.1686 (33%, M^+-iPr[$C_{15}H_{31}O_6Si_2$] = 363.1661), 332.1413 (12%, M^+-iPr-OCH_3), 331.1365 (48%, M^+-iPr-CH_3OH).

4-N-Acetyl-1-[2-O-acetyl-3,5-O-(1,1;3,3-tetraisopropyl)-disilox-1,3-diyl)-β-D-ribofuranosyl]cytosine (145)

To 57 mg (0.1 mmol) of 4-N-acetyl-1-(3,5-O-TPDS-β-D ribofuranosyl)cytosine (144) and 36 mg (0.3 mmol) of DMAP dissolved in 5 ml of anhydrous CH_3CN was added 20 μl (0.2 mmol) of acetic anhydride. After a 3 h period the reaction solution was concentrated *in vacuo*. The residue was subjected to the standard work-up procedure and chromatographed on a column of silica (5 g, 1.5 x 6 cm) using 1% methanol in chloroform as the eluant. Evaporation of the appropriate fractions gave 49 mg (86%) of (145) as an oil with uv (MeOH) max 297 min; 400 MHz nmr δ~1.05 (m, 28, iPr H's), 2.10 (2 x s, 6, 4-N-$COCH_3$, 2'-O-$COCH_3$), 4.00 (m, 3, H-4', H-5', H-5"), 4.43 (d of d, $J_{3'-2'}$ = 5.4 Hz, $J_{3'-4'}$ = 8.6 Hz, 1, H-3'), 5.47 (d, $J_{2'-3'}$ = 5.4 Hz, 1, H-2'), 5.72 (s, 1, H-1'), 7.22 (d, J_{5-6} = 7.6 Hz, 1, H-5), 8.04 (d, J_{5-6} = 7.6 Hz, 1, H-6); M.S. m/z 526.2034 (13%, M^+-iPr[$C_{22}H_{36}N_3O_8Si_2$] = 526.2041), 235.1185 (36%, BHCH=$CHOCOCH_3$), 154.0619 (24%, B+2H), 153.0541 (3.9%, B+H).

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